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THE TUBERCULOSIS PROGRAM OF THE VETERANS' ADMINISTRATION[1]

PAUL R. HAWLEY[2]

The Veterans' Administration is vitally interested in the tuberculosis problems. Having the responsibility for the discovery, the treatment and the rehabilitation of the largest known group of tuberculosis patients, it may be expected, and justifiably so, that we assume the leadership in the fight against this disease. To attain that goal in the shortest time possible, we shall expend all available energies and resources. We do not underestimate the job that lies ahead of us, because we have available to us the picture of what occurred after World War I.

During the period April, 1917 to December, 1919, 12 per cent of the 178,699 discharges for disability, or 22,390, were due to tuberculosis. In World War II up to December 31, 1945, only about 1½ per cent of the discharges for disability were due to tuberculosis. It is estimated that about 150,000 cases of tuberculosis were filtered out by means of chest X-ray examinations at the induction centres.

The peak year for hospital treatment of tuberculous veterans was 1922, when 44,951 patients were treated at a cost of $30,000,000. That year, tuberculosis accounted for 43 per cent of all hospitalized veterans.

Although the pension and compensation rôles climbed steadily from 1919 to 1935, when it reached the total of about 68,000, the hospital beds occupied declined rapidly from the peak of about 11,000 in 1922 to 6,000 in 1927, and tapered off to a low of about 4,000 in 1940. This number again began to rise in 1942 and reached our bed limit in 1945.

At the present time, we have 14 tuberculosis hospitals with a total bed capacity of 5,912. We have tuberculosis units in 14 general hospitals with a total of 1,963 beds and tuberculosis units in 23 neuropsychiatric hospitals with a total of 800 beds, or a grand total of 8,675 beds.

We anticipate the need for 15,000 beds for the peak year 1950. We shall secure these beds by acquisition of Army hospitals and new construction.

The ratio of doctors to patients has been approximarely 1 to 35. These figures have included the various specialists in the hospitals.

We shall employ as many specialists in tuberculosis as we can secure. In our residency program, we shall have a ratio of one resident to 30 patients. To supplement the full-time staff and residents, we shall, when they are available, employ attending men and consultants.

The recruitment of nurses for tuberculosis hospitals has been difficult. The younger nurses have not had much training in the care of the tuberculous. Miss

[1] Presented before the Joint Session of the Medical and Public Health Sections at the 42nd annual meeting of the National Tuberculosis Association, Buffalo, New York, June 13, 1946.

[2] Major General Paul R. Hawley, Surgeon General, Veterans' Administration, Washington, D. C.

Etta McNett is developing aseptic techniques in our hospitals and has already had one of our hospitals accepted for affiliate nurse training. Our aim is to have a ratio of at least one nurse to 5 patients.

We have initiated a program which will prove to be a big factor in tuberculosis case-finding. The program, briefly, is this:

(A) Chest roentgenograms will be secured for each hospitalized patient and every domiciled member at the time of admission and each out-patient at the time of scheduled examinations, if none has been made within six months.
(B) Periodic chest X-ray surveys will be made of all general and neuropsychiatric patients at the end of each twelve months residence in the hospital.

In other words, any veteran who comes to us, will get a chest roentgenogram if he hasn't had one within a period of six months.

We propose to have five types of institutions for the treatment and housing of tuberculous veterans.

1: Tuberculosis units of not less than 100 beds within neuropsychiatric hospitals for the treatment of psychotic tuberculous patients.
2: Sections of not less than 100 beds in general hospitals for the treatment of patients who require constant bed-rest.
3: Convalescent rural sanatoria for patients who are ambulant in any degree and who may be expected to improve with definitive treatment. All of our present tuberculosis hospitals are of this type.
4: Isolated "health resorts" for ambulant patients with positive sputum for whom definitive treatment is inadvisable.
5: Communities for the severely handicapped and for ambulant patients with negative sputum cultures but disabled by emphysema.

Since last December, we have permitted any patient in a Veterans' hospital, who has tuberculosis of service origin, to transfer to and receive treatment at government expense in any hospital with which we can make a contract.

It is our belief that our responsibility for the tuberculous patient is not limited to a period of rest, a minimum of exercise, a classification of an arrested status and then discharge.

If a patient attains an arrested status but is unable to become a useful member of society, he hasn't gained very much, and we have failed in our duty to that patient. It is our intention, if the patient's physical condition permits, to give him the opportunity to become rehabilitated and undergo a period of hardening before he has to go on his own. Each hospital will have a rehabilitation department under the direction of a chief of rehabilitation. The chief of rehabilitation will work in close cooperation with the medical and nursing staffs and all branches of the physical medicine service.

Rehabilitation will begin as early as feasible and will continue until the patient is able to start life anew. We hope to extend his period of full compensability until such time as he may be physically capable of earning his living. There is no logic to taking away the patient's financial aid shortly after he is discharged from the hospital, at the time when he needs it most. The medical profession,

as well as those persons interested in insurance and compensation, is fully aware of the relationship of disability compensation to the speed of complete recovery. Nevertheless, a patient who has religiously pursued the regimen prescribed for him and who is ready to build up gradually to a full-day work tolerance should not have thrust upon him the added financial responsibilities that would result if his pension were reduced or dropped. We believe that delaying this reduction for two years, or until the patient is ready for work, is sound medical practice.

You, no doubt, know that the follow-up care of tuberculous patients by the Veterans' Administration has been practically non-existent. We have inaugurated a follow-up program which I shall give to you in part.

1. In order to enhance and prolong the good effects of hospital treatment among our tuberculous beneficiaries, to discover relapses early and institute treatment promptly, to help prevent advanced disease and to contribute toward safeguarding the health of others through the control of communicable tuberculosis, there shall be instituted an orderly follow-up system of all tuberculous veterans discharged for any reason from a Veterans' Administration hospital, home or centre. Such a follow-up program is intended to ensure continuous medical supervision, reëxamination and appropriate treatment for an indefinite and prolonged period of time, as indicated in the individual case.

2. The responsibility for the care of any tuberculosis patient does not terminate when the patient is discharged from hospital treatment. All of these patients will require further examinations; some will need further treatment and others will need a period of rehabilitation before resuming normal activities.

3. To provide the discharged tuberculosis veteran with the proper follow-up care, the Veterans' Administration will use its available facilities, and will solicit the aid of other agencies interested in the care and rehabilitation of the tuberculous.

4. Under the provisions of present regulations, it is permissible to recall veterans to determine the progress of the disease, with transportation furnished, in those cases where hospital status is clear, and the patient is otherwise entitled. Patients with service-connected tuberculosis can be handled in the out-patient department in many instances without the necessity of admission to the hospital. Patients with non-service-connected tuberculosis, however, will require readmission for check-up purposes. It will be the responsibility of the discharging hospital to make the necessary arrangements with the hospital, or office nearest to the patient's home that is equipped to render such follow-up care, in cases where the veteran is entitled to it but for geographical reasons it is not practicable to have him report to the discharging station.

5. The regional offices may authorize qualified physicians or recognized institutions near a patient's home to render this follow-up care to service-connected tuberculous patients if this is deemed more feasible. Whenever possible, these arrangements will be made prior to the patient's discharge and the patient advised as to which hospital, or office will conduct his future examinations and the approximate date on which he should report for the first one. In the event of departure from the discharging hospital through absence without official per-

mission or discharge against medical advice, which precludes completion of prior arrangements, the patient will be notified by letter of the subsequent arrangements made for his follow-up.

6. In effecting arrangements for follow-up, the discharging station, in the event it will not maintain the follow-up, will promptly forward to the hospital or office which is to continue the treatment the entire file of X-ray films, a summary, including clinical and laboratory findings, the treatment previously received and the examinations or treatment recommended in the future. For those veterans entitled to out-patient service who will not be able to obtain it at a veterans' hospital or office, the necessery arrangements will be made with the regional office having jurisdiction over the case. For those veterans not entitled to out-patient care under existing laws or for whom readmission may not be effected, a report will be sent to the local or State health authorities advising as to the tuberculosis diagnosis, sputum findings, treatment received and the examination and treatment that appear indicated.

7. In these instances, the discharging station will, within a period of thirty days, ascertain from the local or State health authorities whether subsequent contact has been made with the patient by that agency.

8. Great care must be exercised in determining the follow-up care in each individual case. Every patient with active pulmonary tuberculosis should be urged and encouraged to accept hospitalization so that constant observation and supervision may be provided for him. If the patient does not accept hospitalization, the place where the future examinations are to be made and the interval between examinations will be determined to a large extent by the patient's physical condition and the distance from his home to the hospital or office. If the patient's condition may be harmed by traveling, and provided eligibility for out-patient service has been established, every effort shall be made to have the examinations conducted at Government expense in the patient's local community if the proper facilities are available. When proper facilities are not available, managers may assign tuberculosis specialists to conduct the required examinations at the indicated intervals in the local community. Where community hospitals are available, managers are authorized to contract for the use of the X-ray facilities, provided the films become the property of the Veterans' Administration.

9. When it has been determined that the patient is not entitled to out-patient service at Government expense or readmission, he shall be referred to the nearest appropriate community agency which provides that type of care.

To facilitate and expedite the service to the veteran, we have divided the country into 13 areas. In each area we have set up a branch office which is an independent organizational unit of the Veterans' Administration. In each branch office is a tuberculosis division under the direction of a chief and assistant chief of tuberculosis.

It is the responsibility of this division to exercise administrative authority over all of the functions within that branch area which pertain to tuberculosis, including hospital treatment, out-patient treatment, post-hospital follow-up,

examinations and medical decisions pertinent to adjudication. We have appointed 13 outstanding tuberculosis specialists to serve as chiefs of the services. These chiefs are authorized to employ all of the personnel required by the tuberculosis service in their respective branch areas except that final approval for key personnel must be obtained from Central Office. Tuberculosis specialists seeking appointment are given a grade commensurate with their professional qualifications, as determined by a Professional Standards Board. Diplomates of specialty boards will be paid an additional twenty-five per cent.

At the present time, three of our tuberculosis hospitals have been approved for residencies and are under the supervision of medical schools. A number of the general hospitals having large tuberculosis sections are also affiliated with medical schools. All of the new hospitals and tuberculosis sections will be so located that they, too, will be affiliated with medical schools. We hope in the near future to be able to accept interns in these hospitals. We are endeavoring to secure the services of physicians with highest professional qualifications, part-time at least, for the consulting and attending staffs. Plans are now being formulated to establish one or more research centres to provide the means and personnel to study fully the problems of tuberculosis.

There has been established in Central Office a department of "Medical Records and Statistics." Subdivisions of this department will be established in each branch office, regional office, hospital and out-patient clinic, to provide not only the data necessary for efficient operation of an organization of this size, but also data to be used in statistical and other studies.

Every effort will be made to provide the means and the incentive for research. As soon as sufficient personnel has been secured, postgraduate courses for all professional personnel will be encouraged.

In the past, to promote a worthy employee, it was first necessary that a vacancy in a higher position be found. If no vacancy occurred, no promotion could be accomplished. After a certain grade was reached, to promote a competent clinician, it was necessary to put him into an administrative position if a vacancy existed. This system of promotion lowered the morale of the energetic, dynamic type of individual and was not conducive to meritorious efforts.

We have changed the system of promotions. At periodic intervals, there will be a review of each employee's record. If his performance of duty justifies it, he will be promoted and he will continue performing the duties he is most qualified to do and for which he, no doubt, has shown a preference. If an employee's service has been unsatisfactory, he will be separated from the service.

By these means we shall raise the morale of all, *esprit de corps*. We shall offer encouragement for improvement to each individual, thereby effecting improvement of the entire Department of Medicine and Surgery, and it will manifest itself in the service rendered to the veteran. We also hope to contribute at least our share toward the advancement of medical science.

I take this opportunity to express to the National Tuberculosis Association and to each of you individually my sincere appreciation of the coöperation you have shown in the past and I hope to receive your fullest support in the future.

SUMMARY

Responsible for the largest known group of tuberculosis patients, the Veterans' Administration may be expected to assume leadership in the fight against this disease. For the peak year of 1950, a need for 15,000 beds is anticipated and this requirement is being met through acquisition of Army hospitals and new construction. The present bed capacity is approximately 6,000.

The ratio of doctors to patients, including various specialists, has been set at approximately 1 to 35 and a goal has been fixed for at least one nurse to 5 patients.

Through a tuberculosis case-finding program, any veteran who comes to the Veterans' Administration will get a chest X-ray examination if he has not had one within the past six months.

Tuberculous patients will be treated at five types of institutions: (*1*) tuberculosis units within neuropsychiatric hospitals; (*2*) sections of not less than 100 beds in general hospitals; (*3*) convalescent rural sanatoria for ambulant patients; (*4*) isolated "health resorts" for patients with positive sputum but for whom definitive treatment is inadvisable; and (*5*) communities for severely handicapped, but ambulant, patients with negative sputum.

Rehabilitation is important in treatment. When ready, a patient is aided to become a useful member of society again while still in the hospital.

To provide orderly follow-up care of tuberculous patients, the Veterans' Administration is coöperating with other agencies in an effort to enhance and prolong the good effects of hospital treatment and to contribute toward safeguarding the health of others. Such a program is intended to ensure continuous medical supervision. Responsibility for the care of the tuberculous does not end when the patient is discharged from hospital treatment.

To improve medical service to the veteran, outstanding tuberculosis specialists serve as chiefs of services at each of the 13 branch offices Morale of all Veterans' Administration physicians has been raised by a change in the promotion system which now provides promotion on the basis of background and performance, not on whether a vacancy exists in a higher position.

SUMARIO

Teniendo a su cargo el mayor grupo conocido de tuberculosos, cabe esperar que la Administración de Veteranos tome la delantera en la lucha contra esa enfermedad. Para el año cumbre de 1950, anticípase que se necesitarán 15,000 camas, y se va atendiendo a ese requisito mediante la adquisición de hospitales militares y la construcción de otros nuevos. La capacidad actual es de unas 6,000 camas.

La proporción de doctores, incluso especialistas, en relación con los enfermos, ha sido fijada aproximadamente a 1 por 35, y la meta para enfermeras es como mínimo 1 por 5.

Mediante un plan de descubrimiento de casos, a todo veterano que se presente a la Administración de Veteranos se le hará un examen radiográfico del tórax si no le han hecho uno en término de los 6 meses anteriores.

Los tuberculosos serán tratados en cinco clases de instituciones: (1) unidades para tuberculosos en hospitales neuropsiquiátricos; (2) secciones de menos de 100 camas en hospitales generales; (3) sanatorios rurales de convalecencia para ambulantes; (4) "casas de salud" aisladas para enfermos con esputo positivo en los que no conviene un tratamiento preciso; y (5) centros destinados a enfermos bastante incapacitados, pero ambulantes, con esputo negativo.

La rehabilitación es importante en el tratamiento: Cuando llega el momento, y aun estando el enfermo en el hospital, se le ayuda a volver a ser un miembro útil de la sociedad.

A fin de facilitar asistencia subsiguiente metódica a los tuberculosos, la Administración de Veteranos coopera con otros organismos para acrecentar y prolongar los buenos efectos del tratamiento hospitalario y ayudar a salvaguardar la salud ajena. Ese plan se propone asegurar continua vigilancia médica, pues el deber de asistir al tuberculoso no termina cuando se le da de alta del hospital.

Con mira a mejorar el servicio médico prestado a los enfermos, eminentes tisiólogos actúan como jefes de servicio en cada una de las 13 filiales. El espíritu de todos los médicos de la Administración de Veteranos ha sido realzado por un cambio en el sistema de ascensos, basado en la preparación y ejecución del individuo y no en si existe una plaza superior vacante.

THE NATIONAL TUBERCULOSIS ASSOCIATION AND ITS INTEREST IN THE TUBERCULOUS VETERAN[1]

HERBERT R. EDWARDS[2, 3]

The interest of the National Tuberculosis Association in the tuberculous veteran dates back to 1916. During and following the World War, the Association contributed generously of its resources to bring about the maximum in care for the veteran, and to prevent, as far as possible, the conditions and situations that loomed so menacingly at the beginning of the world conflict only recently closed.

It is of interest, therefore, to review briefly the problem as it was visualized prior to, during and after the first World War and note the policies adopted for their solution and their possible relationship to the problem in 1943, when the Association again appointed a committee to study the situation and make recommendations.

In May of 1924, the Association published a booklet *Cooperation, a Summary Report on the Activities of the National Tuberculosis Association for Tuberculous Servicemen in Cooperation with the Federal Government.* This booklet recounts many interesting facts dating from 1916 up until the time of its publication. They are discussed under six major headings as follows:

1: Compensation for physical disability.
2: Hospitalization.
3: Training of personnel.
4: Rehabilitation.
5: After care.
6: Education, publicity and legislation.

The Association assisted the government by the appointment of some ten committees that dealt with these problems and by the loan of members of its staff to do the large amount of field work involved. Of the latter, Dr. H. A. Pattison and Mr. T. B. Kidner contributed heavily of their time to the work of the various committees. On the committees were found a notable list of the outstanding tuberculosis physicians of the day.

In the latter part of 1916, Landouzy reported a frightful toll of lives sacrificed because of tuberculosis in the French Army. It was Herman Biggs, who, on the basis of his own observations in France, aroused the interest of the Association in the problem as it might affect the armed forces of this country. The annual meeting of the Association held in Cincinnati in 1917 was literally a war meeting,

[1] Presented before the Joint Session of the Medical and Public Health Sections at the 42nd annual meeting of the National Tuberculosis Association, Buffalo, New York, June 13, 1946.

[2] Director, Bureau of Tuberculosis, New York City Department of Health, 125 Worth Street, New York, New York.

[3] Chairman, Committee on Tuberculosis among Veterans, National Tuberculosis Association.

and it was there that Biggs epitomized the general attitude in the following words: "So far as I know, tuberculosis has never before played a very large part in the sanitary history of any great war, but it is playing such a part in the present struggle." This prophecy was borne out to a degree that was not fully realized at that time, and we are still paying to-day for that situation.

COMPENSATION FOR PHYSICAL DISABILITY

The Executive Committee of the National Tuberculosis Association in July, 1917 went on record as endorsing the principle of separation allowances to be provided by Federal legislation, and of compensation for the injuries, sickness and death resulting from war. A committee was appointed to further legislation to these ends.

The Congress of the United States enacted into law an act, on October 6, 1917, that created the Bureau of War Risk Insurance. There were three chief features of this Act.

A. "A deviation from the established policy with reference to wholesale granting of pension to ex-servicemen, and a substitution for this policy of one of compensation based upon the degree of injury or disability."

B. "The provision of hospital care as a distinct part of a wounded or sick soldier's compensation."

C. "The provision of vocational training in an effort to rehabilitate the sick or injured veteran along lines commensurate with his physical impairment."

On March 5, 1915, the National Association adopted a resolution dealing with the degree of disability of tuberculosis and the amount of rating essential for compensation, a problem that grew out of the War Risk Insurance Act. The resolution was as follows: "That a man with proven tuberculosis is entitled to compensation, the minimum rate of which to be not less than 25 per cent." The substance of this resolution was adopted by the government.

In May of 1922, the National Association supported a resolution presented by Dr. F. M. Rinehart, Clinical Director of Tuberculosis of the United States Veterans Bureau, the effect of which was to limit the cash compensation allowed to tuberculous patients during the period of hospitalization, and to set aside the main portion of their legal allotment as a fund to accumulate against the day of discharge from the hospital, and for the maintenance of their families, if any, during treatment. The Advisory Committee of the Veterans Bureau, a committee appointed by the National Tuberculosis Association, at the request of the Director of the Bureau, also urged such an amendment to the compensation law. Another Advisory Committee appointed to the O'Ryan Investigating Committee in 1923, urged a similar amendment. These recommendations were not adopted.

The National Association and committees appointed by it, at the request of the government, coöperated in forming various regulations dealing with rating cases of tuberculosis. They offered suggestions dealing with Boards of Consultants, time limits for compensation and the important subject of discipline in compensation.

In this latter matter, it became obvious that the best interest of the veterans

was not being served by the comparatively large sums of money available to him. There was every reason to believe that these funds, with free hospital care and treatment, tended to be subversive to discipline. An appeal was made by the Association to the government, to the American Legion, to the press and to the general public, to change the compensation act in order to promote discipline and provide proper regimen in the treatment of tuberculosis. The act was amended in such a manner that the compensation of the ex-serviceman could be reduced or withheld temporarily in order to discipline him to observe the regimens necessary to take care of tuberculosis.

HOSPITALIZATION

The history of hospitalization for the veteran is long and involved, and we only need to note here that when the United States entered World War I in 1917, it was relatively unprepared to meet the demands that were a logical sequence to the Acts of the Bureau of War Risk Insurance. All told, there were only 1,000 beds for the tuberculous controlled by the Army, U. S. P. H. S. and the National Soldiers Home, with a possible additional 1,000 available for cases of emergency.

It was not until December 5, 1919, that the historic document, #481, was submitted to Congress. It was a plan to provide care for disabled soldiers and sailors. This document was submitted together with a bill providing for a total appropriation of little over $185,000,000.00. Considerable discussion in and out of Congress followed, with the general theme of building large government institutions.

This viewpoint was not approved by the National Association and they set about trying to get backing for the utilization and expansion of existing tuberculosis hospitals as a more realistic approach to the problem. The position of the National Association was overruled, due to the desire of certain members of Congress, who, for political and other reasons, wished to have hospitals located in their districts. Similar opposition was voiced by the American Legion, which organization apparently did not fully appreciate the true meaning of the National Association's attitude.

On March 4, 1921, two years after the first attempt to make hospital provision, and three and a half years after the original promise of October 6, 1917, Congress enacted a law that gave promise of a real institutional plan to take care of the ex-servicemen. Following this action, the Secretary of the Treasury, the Honorable A. W. Mellon, appointed a small Advisory Committee of consultants composed of the following men: Dr. William Charles White, Chairman; Dr. Frank Billings; Dr. John C. Bowman; Dr. Pearce Bailey, later succeeded by Dr. George H. Kirby. To assist the committee, the National Association assigned Dr. H. A. Pattison of the medical service and Mr. T. B. Kidner, institutional secretary of the National Association. They spent approximately two years visiting hospitals or proposed sites for the committee. Standard plans for hospital construction were prepared, and studies of the relationships of federal, local, state, county and municipal institutions were made, and the possibilities of adding to existing governmental institutions were explored. This committee reiterated its inten-

tion that the Veterans Bureau should not build institutions "merely to satisfy the desire of patients or the demands of political and commercial constituents."

In November, 1922, the Advisory Committee of the Veterans Bureau recommended that the occupational training of ambulant tuberculosis patients should be conducted in connection with an institution, where continuous and uninterrupted medical supervision would be available.

At this time, there was a growing tendency toward lay domination in the administration of tuberculosis hospitals. The Advisory Committee, on May 2, 1922, resolved "That the administration of hospitals for the treatment of the tuberculous is chiefly a medical problem of a highly technical character. Therefore, the control of professional personnel in the hospitals of the Veterans Bureau as to appointment, transfer or discharge, should be vested in the medical director of the Veterans Bureau..."

PERSONNEL

The Executive Committee of the National Association, on January 7, 1920, strongly urged "the justice and necessity for increased salaries for the personnel of the U. S. P. H. S., to insure successful and adequate care of the tuberculous ex-soldier and ex-sailor and all other persons entitled to such care.

"In regard to the training of personnel, the National Association has repeatedly urged the development of schools for the training of doctors, nurses and other paid officials dealing with the tuberculous ex-serviceman. The National Association has urged generally that for medical officers, special training in diagnosis and treatment be provided by the Veterans Bureau of not less than six months, and preferably one year's duration."

In commenting on this matter, General Hines indicated his whole-hearted accord in the imperative need for thorough training, but felt that it would never be possible to extend courses for the time limit proposed without disrupting the routine work of the Bureau.

REHABILITATION

The National Association, in November, 1918, assigned Dr. H. A. Pattison for seven months to develop a plan for vocational training of the tuberculous veteran. Considerable progress was made, and it is obvious that the interest stimulated by the Association had a far-reaching effect, even though the program was never entirely satisfactory.

AFTER-CARE AND HOME TREATMENT

At the request of General John O'Ryan, acting as Counsel for the Special Committee of the United States Senate investigating the Veterans Bureau, a committee was appointed to consider the after-care of the general problem of hospitalization. This was early in 1922, and the following significant suggestions were made:

1: That home treatment is impractical and inadvisable.

2: That the cottage or one-man type of hospital by which a patient might be allowed to hospitalize himself, is not proper hospital treatment.

3: That sanatorium and hospital treatment is the best method of treating tuberculosis.

4: That special diagnostic services in each district for cases of doubtful diagnosis should be provided.

5: That extension courses of training should be provided.

6: That existing social service agencies should be utilized.

7: That repeated follow-up diagnoses be made, and that records be centralized, so that a case can be followed from its beginning to its completion.

8: That conferences between divisions be held on matters dealing with these situations.

EDUCATIONAL ACTIVITIES

The educational activities of the Association were originally conceived as twofold: First, towards the men, and secondly, towards the government or officials endeavoring to solve the problem of tuberculosis. All available avenues were utilized in the former, and the preceding comments indicate the mode of coöperation in the latter. These same principles have, in the years since, actuated the policies and services of this Association, not only towards the veteran but to the community at large.

The foregoing services and the objectives of the National Association for the period 1916–1924 are important, because they indicate quite clearly the accepted thinking on these policies at that time, and they represent basically the concepts for the solution of the problem as we see it to-day. Had more of these concepts been adopted, and had they become an integral part of the Veterans' Administration in the years between the two great wars, it is reasonable to believe that the Veterans' Bureau in 1943 would have been better prepared to meet its new responsibility imposed by World War II.

Some of the major difficulties, from the standpoint of medical services rendered to veterans, have been the organizational barriers interposed between the Medical Director and the Administrator. A Committee of the National Association, under the chairmanship of Dr. David Lyman, in 1934, reported in part as follows: "There are about eight main bureaus under General Hines. Every one of these bureaus is headed by a layman. Under one of these lay bureaus is the director of the medical service. His one approach to the head of the bureau on any medical problem is to go through the layman who is over him, and then, if it is very important, that layman can go directly to General Hines, but most routine matters go through aides of General Hines. Any medical matters to be initiated, any educational or clinical work, anything to do with rating of cases, coming from this medical man has to get the okay of one or two of these laymen before the medical staff can move a hand."

Despite recommendations to change this situation, the same organizational plan continued until the recent reorganization of the services in 1945.

THE PROBLEM IN 1943

The entrance of the United States into the recent world conflict immediately brought to the fore the possibility of a marked increase in the number of veterans

who would develop tuberculosis and be in need of modern therapy. In retrospect, it was obvious that the previous system had not functioned adequately, and there was every reason to believe that the application of present-day concepts could not only reduce the cases that would need care, but could also assure a much higher degree of permanent arrest and cure, if a way could be found to apply them.

The first step in this direction was the inclusion of a chest roentgenogram as part of the routine examination of all Selectees. This procedure would weed out as thoroughly as possible persons with potentially active, as well as active disease. The contribution of this procedure in tuberculosis control is too well known to warrant extended discussion here. It was realized that despite this effort, some men with lesions would be taken into the service, and furthermore, many would develop a lesion as the result of the rigors of training and war. Thus, the Veterans' Administration should plan for an increase in its tuberculosis problem, that would, on the whole, be found among a younger age group than the World War veteran then under care.

The Committee on Tuberculosis among Veterans of the National Tuberculosis Association was organized in the spring of 1943, at a time when there were current an increasing number of reports indicating a questionable quality of medical service to the tuberculous veteran. The immediate problem concerning the Committee was the determination of the cause or causes that underlie the refusal of patients to accept medical care in veterans hospitals, or once admitted, their refusal to continue treatment to the point of maximum hospital benefit. It was the feeling of the Committee that the aforementioned causes might be revealed by exploration into the following fields:

1: Medical organization of the Veterans' Administration.
2: Selection, assignment, promotion and training of professional personnel.
3: The geographic location of hospitals as related to medical teaching centers and convenience of patients.
4: The effect of the existing pension plan on the contentment of the veteran.
5: The relationship of the Veterans' Administration to the following:
  (*a*) Veterans' organizations.
  (*b*) Public health agencies.
  (*c*) Voluntary health agencies.

In consideration of the foregoing rather broad concepts, it was decided that, as far as possible, each medical member of the Committee should observe at first hand the clinical administrative practices in as many tuberculosis hospitals as possible within the limited time available. A few members of the Committee went to General Hines on October 31, 1944, to solicit his coöperation and to outline their proposed method of study. At this meeting, General Hines assured us of full coöperation on the part of his staff, and we were accorded every possible courtesy by the personnel in the Washington office, as well as by the personnel in the various Facilities. Conferences with individual members of the staff were conducted on a confidential basis, and it is believed that the Committee obtained an accurate insight into the problem.

THE SCOPE OF OBSERVATIONS OF THE COMMITTEE

1. *Evaluation of veterans hospitals:* Visits were made to 17 hospitals scattered throughout the country. Observations were made according to an accepted outline, so that our findings might be as nearly comparable as possible. The findings of each member for each institution visited were circulated to other members of the Committee and formed the basis for our subsequent discussions and recommendations.

2. *Evaluation of published reports on the veterans problem:* Careful consideration was given to an increasing volume of reports, by professional as well as by lay writers, with the result that the Committee felt that, for the most part, they were subject to reëvaluation, if a purely objective viewpoint were to be followed.

3. *Laws, rules and regulations governing medical services:* Considerable time was devoted to the policies of considerable volume of the aforementioned material, because it represented the rules and regulations under which the veterans law was being administered, and very likely determined the type of service to be found in the hospitals. Considerable assistance was obtained by Mrs. Mary Mack of the National Association's staff, who was engaged at that time in codifying this type of material.

4. *Social service and rehabilitation:* Recognizing that rehabilitation, as a part of the medical scheme for the tuberculous veteran, was of the utmost importance, the Committee had the counsel and advice of the Rehabilitation Service of the National Association, which had had members of its staff in some 21 different veterans hospitals where careful studies had been made. Thus, we were privileged to review the studies and opinions of experts in this important field.

5. *Utilization of facilities of veterans' organizations:* The national veterans organizations, as early as 1943, declared themselves in favor of greater effort by their affiliates, to convince the veteran of the importance of his remaining in the hospital until he had received the maximum benefit. This thought was in line with the attitude of the National Tuberculosis Association and its various affiliated associations throughout the nation. As a consequence, the National Association's local committees have made a nation-wide effort to implement the declaration of the national organizations for veterans, and immediately many valuable contacts were made in various states to set up educational programs.

RESULTS OF STUDY

The results of the study made by this Committee are of interest or importance only as they represent the situation that existed prior to the reorganization of the Veterans' Administration under General Bradley. The profound changes that have been initiated in the few months of his incumbency are in line with the Committee's recommendations. Our interest, therefore, is more concerned with the further development of his plans than it is with the review of past accomplishments or delinquencies. It is important to point out that these new objectives will not be realized to the full without the expenditure of considerable time and effort, both now and for many months to come. Already a number of leading tuberculosis clinicians and administrators have accepted assignments in the

Veterans' Administration, and this will tend to attract still others to a service that in fact may become a real service in the true sense of the word.

The problem of tuberculosis among veterans must not be viewed as the exclusive responsibility of the Veterans' Administration. The veteran is also a citizen, and, therefore, he is a problem of the community in which he lives. There is a clearly indicated need for a far closer relationship between the Veterans' Administration and the various departments of health, state and local, throughout the country. The outlook for an improvement in this relationship is most encouraging. The veterans' hospitals are reporting promptly all tuberculosis cases at the time of admission and discharge, which gives the local health authority an opportunity to set in motion local control facilities. This will be considerably augmented with the expansion of tuberculosis control facilities in many states and communities through the efforts of the U.S. Public Health Service and its Division of Tuberculosis Control. Thus, there is every reason to believe that, as time passes, we will come nearer and nearer a uniform procedure of practice in all states and communities.

The voluntary agencies, such as the veterans' organizations and their auxiliaries, the tuberculosis associations and such other agencies as are interested in the veteran and tuberculosis, have not only an opportunity, but a responsibility as well to contribute to the cause. These organizations acting in a concerted fashion can be of the utmost importance in furthering the present reorganization now under way. The accomplishment of the goals that have been set is only a part of the job. We must make sure, so long as there is need for such services in the future, that the same high type of service will continue. The opportunities of these organizations to disseminate health education and to formulate public opinion, if intelligently used, should assure us of the accomplishment of our objectives in the shortest possible time.

SUMMARY

A brief review of the interest and activities of the National Tuberculosis Association in behalf of the tuberculous veteran has been presented. Basically, the recommendations of the Association have been to create a medical service of the highest possible caliber. Rehabilitztion was visualized as an important adjunct to the proper arrestment of the disease and as a method to prevent repeated relapses that have been so common in veterans of the first World War.

The Association appointed a Committe in 1943 to reëvaluate the situation and make recommendations for improvement. This Committee had the full support and coöperation of the Administrator of veterans' affairs. Some 17 different hospitals were visited and the observations made formed the basis of a report to the Administrator.

In addition to the specific recommendations for improved medical care and rehabilitation for the veteran, the Committee visualized the tuberculous veteran as a problem not only belonging to the Veterans' Administration, but as well a problem of the community in which he resides. Local health departments, tuberculosis associations, veterans organizations and others, interested in the

control of tuberculosis, have a definite responsibility which, if constructively developed, can contribute materially to the continued well-being of the veteran.

The recent reorganization of the Veterans' Administration under General Bradley and the events that have developed since that time have indicated that the recommendations of the Committee are being adopted as rapidly as possible.

SUMARIO

Esta breve reseña describe los esfuerzos y obras de la Asociación Nacional contra la Tuberculosis en pro del veterano tuberculoso. En el fondo las recomendaciones hechas han tenido por mira la creación de un servicio médico de la mejor calidad posible, visualizando la rehabilitación como importante coadyuvante del estacionamiento adecuado de la enfermedad y como método destinado a impedir las recidivas repetidas que han sido tan frecuentes entre los veteranos de la I Guerra Mundial.

La Asociación designó en 1943 una Comisión que justipreciara de nuevo la situación y formulara recomendaciones encaminadas a mejorarla. Esa Comisión recibió pleno apoyo y cooperación de parte del Administrator de los asuntos de veteranos. Unos 17 hospitales fueron visitados y las observaciones realizadas en ellos formaron la base de un informe elevado al Administrador.

Además de sus recomendaciones específicas en cuanto a mejor asistencia médica y rehabilitación para el veterano, la Comisión consideró al veterano tuberculoso como problema que interesa no sólo a la Administración de Veteranos sino a la colectivitad en que aquél reside. Los departamentos locales de sanidad, las asociaciones antituberculosas, las ligas de veteranos y otros interesados en la lucha antituberculosa tienen una obligación bien definida, que si se desempeña constructivamente, puede contribuir decididamente al continuo bienestar de veterano.

La reciente reorganización de la Administración de Veteranos bajo la dirección del General Bradley y los desenvolvimientos desde entonces indican que las recomendaciones de la Comisión van siendo puestas en efecto con la mayor rapidez posible.

RECENT DEVELOPMENTS IN TUBERCULOSIS CONTROL[1]

HERMAN E. HILLEBOE[2]

Since its inception in July, 1944, the Tuberculosis Control Division of the United States Public Health Service has made many advances toward a realization of its long-range objectives—the eradication of tuberculosis in the United States. At the beginning of its work, measures were instituted to study the scope of the tuberculosis problem and to organize the new Division into efficient and integrated Sections. Because the work of the Division necessarily had to include all types of service and research and because the major portion of this enterprise would require coöperation with State and private health agencies, four sections were organized at the outset, Administrative, State Aid, Field Studies, Radiology, and their activities and their objectives were specifically stated.

During its first year of operation, the Division occupied itself with the recruitment and training of personnel, with the development and actual operation of the grants-in-aid program and the procurement of necessary field and laboratory equipment. The requirements of a national program were studied and plans were made to satisfy the many demands from the State and local health departments Grants-in-aid funds during this first year were used by the States mainly for the purchase of equipment and supplies for case-finding, and the establishment of follow-up services, including recruitment and training of professional personnel. The Division participated in these State functions through consultations, demonstrations and the loan of professionally trained persons.

During the fiscal year 1946, the Tuberculosis Control Division participated in organization and integration of tuberculosis control activities in almost every State of the Union. By means of new X-ray film techniques, the Division demonstrated the feasibility of X-raying the majority of the adult population in the United States and the possibility of actually starting on a program of eradicating tuberculosis.

Until the establishment of the Tuberculosis Control Division, programs against tuberculosis were conducted largely by voluntary agencies led by the National Tuberculosis Association, which emphasized health education and legislation, and by State and local health departments. The Tuberculosis Control Division in no sense replaces any of these groups; rather it is the function and the purpose of the Division to guide and to coordinate by means of technical, advisory, research and financial aids all existing agencies which are working toward the goal of eradication. Now at the end of its second year of activity the Division can demonstrate material progress. Its four major objectives, case-

[1] Presented before the Joint Session of the Medical and Public Health Sections at the 42nd annual meeting of the National Tuberculosis Association, Buffalo, New York, June 13, 1946.

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finding, medical care and isolation, after-care and rehabilitation, and protection of the tuberculous family against economic distress, have been guiding principles which are beginning to produce results and have created policies and procedures for the future.

By the end of its first year of operation the Tuberculosis Control Division had found case-finding to be eminently successful. Its major tool, the small-film X-ray machine, permitted the examination of large population groups, whereas before this instrument was brought to its present state of development only individuals and families could be reached by the large-size X-ray equipment. Now the X-ray goes to the people in their own communities, examines them in large groups and discovers tuberculosis in its minimal stage. Tuberculosis is being found when it can be readily arrested, sometimes without hospital care. In recent years only 10 to 15 per cent of admissions to tuberculosis hospitals had minimal disease. To-day with modern case-finding techniques 65 to 70 per cent of all case found are in the minimal stages. In this way it has been demonstrated to the local communities that tuberculosis can be controlled, if cases are followed up after discovery by these modern methods. Future efforts must be reinforced by vigorous community accomplishment in medical care and hospitalization of all newly discovered cases. The services of official and voluntary agencies must be brought closer to the people. That is our intention and objective in the coming years.

In terms of nursing, clinic care and mass case-finding, our services are even now reaching the people in local communities. Field demonstrations have been set up; coöperative research has been started; recruitment and training of personnel has gone forward; and grants-in-aid have been widely used. The Division has more than 20 field case-finding and follow-up units which are sent where they are specially needed, upon request of State and local health departments unable to procure such equipment and personnel. Concurrent with the activities of these photofluorographic units, the Division has trained and assigned medical officers to 40 of the 48 States. In carrying out its policy of coöperation with States, the Tuberculosis Control Division has expanded its activities beyond case-finding and has assisted in the establishment of clinics, laboratories, nursing services and research.

The Division has repeatedly urged more facilities and personnel for after-care and rehabilitation. There can be little value in finding a patient with tuberculosis if he is not given medical care and if he is not isolated. It is equally certain that a tuberculous person whose disease has been arrested must be helped in returning to normal life. Moreover, it is plain that the patient's family must not be permitted to suffer and become a burden upon the community when the breadwinner is detained in the hospital.

Immediately after its organization the Division instituted a number of coöperative research projects which are already producing significant results. The more important of these undertakings have included studies in minimal lesions and pulmonary fungus infection, in coöperation with the Medical Research Com-

mittee of the National Tuberculosis Association, the University of Kansas, the Kansas City, Missouri and the Kansas State Health Departments. Mortality studies are being done in coöperation with the Bureau of the Census. Studies are going forward in coöperation with the University of Michigan on methods of reproducing X-ray films, investigations into the use of mass radiography in general hospitals, and researches in experimental radiology. Follow-up studies, with Temple University, of patients discovered to have minimal tuberculosis in industrial surveys are now under way. Studies are being developed in our own laboratories in Maryland on the electronic amplification of the fluorescent image and its use in photofluorography. The electronic laboratory of the Division in Rockville, Maryland, coöperates with the National Electric Manufacturers Association in studies on standardization of photofluorography. In addition, the Division materially encourages fundamental research in an unrelenting effort to discover a drug that will be effective against the tubercle bacillus.

Many grave problems confront us in the fight against tuberculosis in the United States. We must know more about the mode of spread of this disease. We must know why it selects certain age groups and races. Certainly we must learn the secrets of its successful defense against every drug and biological now known. Extensive collaborative research firmly directed, adequately financed and carried forward by the teamwork of many men and agencies must be initiated in even larger measure than before if tuberculosis is to be eradicated.

During fiscal years 1947 and 1948, the Tuberculosis Control Division hopes to reach the planned level of operation which, from the beginning, was its goal; this provides $8,500,000 for grants-in-aid and $1,500,000 for demonstrations, research and training of personnel. Appropriated monies will be used principally to augment local activities through grants-in-aid and, in part, for consultation purposes by experts in such fields as medical social work, rehabilitation, nursing and clinic care. Research in chemotherapy will be expanded; new demonstrations carried on in local communities; grants-in-aid will be increased to give more actual service to tuberculous patients in local communities.

It must be remembered that the Federal Government, State governments and local communities spend from 75 to 100 million dollars in maintenance and operation of tuberculosis hospitals and sanatoria each year. In spite of this large expenditure for the maintenance of 80,000 beds, there is still a shortage of 40,000 to 50,000 beds for the tuberculous in the United States. Individual States are unable to pay the whole construction cost. Adequate assistance from the Federal Government is essential for the construction of a sufficient number of beds to meet minimum requirements. This is a problem that we must face at once.

Reported figures show that tuberculosis mortality is steadily but slowly on the decline; however, we must not rest in false comfort in the face of expected diminishing returns. The present tempo of the tuberculosis control program must be increased greatly if we are to use our full knowledge in the control of the disease and speed up the rate of decline of tuberculosis deaths. Tuberculosis does not respect State boundaries. It cannot be stopped by a strong program in one

State if there is a weak program in another. Throughout the country, a program of control must be uniformly strong. Combined adequate resources of official and voluntary groups will bring us to this objective.

Within the next five years the Tuberculosis Control Division will continue its case-finding and follow-up program and will set as its goal examination of the majority of persons over 15 years of age in the population of the United States. Such an intensive campaign will make necessary increased efforts in providing simultaneously medical care and isolation, after-care and rehabilitation and protection of the patient's family against economic distress. These objectives can be attained in that relatively short period. Then the stage will be set for the final eradication of tuberculosis in the United States.

TUBERCULOSIS AS AN INTERNATIONAL PROBLEM[1,2]

JAMES A. DOULL[3]

The Health Conference of the United Nations will commence its deliberations in New York next week. The task assigned to it is the preparation of a constitution for a new international health organization. As a basis for discussion Draft Proposals have been prepared by a group of public health experts appointed by the Economic and Social Council, one of the constituent organs of the United Nations. The suggested name is the World Health Organization. For greater freedom of action, it is recommended that the organization should be a specialized agency rather than a constituent part of the Economic and Social Council having, however, a close relationship to the Council established by mutual agreement.

At the same time a movement is on foot to reactivate the International Union against tuberculosis. The Union is the successor of the Central Bureau for the Prevention of Consumption which promoted six international congresses between 1899 and 1908. The Bureau had its headquarters in Berlin and consequently it became an incidental casualty of the First World War. Efforts to revive it failed, and the Union was established in 1920. Ten Conferences were held under the auspices of the Union and in 1938 its membership included either the National Tuberculosis Associations or the governments of 44 countries.

It is timely, therefore, to press the urgency of international action in this field and in particular to discuss the activities which might be undertaken respectively by the new international health organization and by the Union. The former will be an inter-governmental organization. The Union may be regarded as a non-governmental agency although about one-third of the countries included in its membership have government representatives because they do not have national tuberculosis associations.

It is appropriate also that this subject should be brought to the attention of the National Tuberculosis Association. The Association has always taken a lively interest in the international aspects of tuberculosis. It was chiefly responsible for the success of the Washington Congress of 1908, the greatest tuberculosis congress in history. It was a foundation member and has been a continuous supporter of the Union. Also through the AMERICAN REVIEW OF TUBERCULOSIS it has exerted a stimulating influence on research throughout the world.

The Draft Proposals envisage broad functions for the World Health Organiza-

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[2] Published by permission of the Surgeon General, United States Public Health Service.

[3] Chief, Office of International Health Relations, U. S. Public Health Service, Washington, D. C.

tion. It is recommended that the International Office of Public Health at Paris should be absorbed and that existing regional intergovernmental health agencies should be integrated into the world system. With the taking over of the League of Nations by the United Nations, the Health Organization of the League, as such, will cease to exist but doubtless many of its former activities will be undertaken by the new organization.

The old idea that practicable quarantine measures can prevent transmission of infectious diseases by international commerce dies hard, as does the related concept that administration of such quarantine measures is the chief function of an international health agency. The Proposals are modern and realistic. It is recognized that, although it may be necessary to take control measures at certain boundaries for many years, especially to prevent the introduction of exotic insect vectors of disease, the objective of quarantine can be attained only by eradication of infectious diseases at their sources. Consequently emphasis is placed upon the strengthening of national health services. The Health Organization of the League had entered this sphere of activity, especially in China and Greece, and would have gone farther had it received necessary financial support. The Proposals clearly indicate that the World Health Organization can assist a member nation only by invitation. Nevertheless there will be some fear of infringement of national sovereignty, especially at the outset. This fear, together with the misconception regarding the true value of quarantine, must be overcome if international health work is to be really effective.

What is needed, in effect, is a new definition of the word "international" as applied to health problems. Fundamentally it would appear that a health condition has international implications under any of the following circumstances:

1: It threatens the safety of other nations.
2: It is exceptionally serious in certain countries and demands consideration because of economic or humanitarian aspects.
3: It is caused or accentuated by causes beyond the control of any single nation.

Tuberculosis rarely occurs in epidemics and cannot, therefore, be considered to constitute a direct threat to other nations. Nevertheless, it is easy to establish an irrefutable case for official international action. The basic reasons are each well known but it is useful to assemble them.

1. In the first place, because of peculiarities in its pathology and epidemiology, tuberculosis, especially the pulmonary form, has attained world-wide prevalence. The mode of transmission is simple and while there are great variations in susceptibility, no class or subdivision of mankind is immune. These peculiarities make it reasonably certain that no nation could eradicate the disease and by artificial barriers of any kind prevent its introduction from without. Even if such procedures were theoretically possible, the limitations which they would place upon travel and commerce would make them impracticable.

2. In the second place, tuberculosis constitutes a humanitarian problem of great magnitude. The most recent comprehensive review, that of the United

States Census Bureau in 1938, includes mortality figures for only 32 nations. The rates varied from 40 per 100,000 to 260. For a large part of the world's population, tuberculosis deaths are unrecognized, uncounted or both. It is impossible, therefore, to make more than the roughest estimate of the toll which the disease exacts. It is safe to say, however, that there occur each year in the world more than three million deaths from all forms of tuberculosis and that the total probably exceeds five million.

3. In the third place, while tuberculosis is often stated to be a consequence of poverty, it is in itself a cause of great economic loss. This is a result not only of the very high rates of prevalence which prevail in many countries but also of the peculiar age selectivity of the disease. It affects men and women in their most productive years, and at ages when they are most likely to have dependents. The immediate loss, therefore, is but part of the picture. The social illness continues long after that of the individual terminates.

4. In the fourth place, world events, beyond the control of any single nation, may affect seriously a nation's tuberculosis rate. Among these are:

(*a*) Curtailment of food supplies. Recent world shortages have accentuated the dependence of the peoples of the world upon one another for wheat, fats and other essential food.

(*b*) Great epidemics. The great influenza epidemic of 1918 caused a great increase in the tuberculosis death rate through the world.

(*c*) War. Apart from the effect of the influenza epidemic, the First World War caused some increase in tuberculosis in several countries. The greatest effect was observed in large cities of Germany and Austria after the collapse of the German army.

We are now learning something of the effect of the Second World War. Statistics are very deficient; in fact they are reliable only for those countries which in all probability were the least affected.

In England and Wales and in Scotland not only was the prewar downward trend arrested but a considerable increase occurred, especially in nonrespiratory forms of the disease. The peak was reached about 1941 after which mortality declined. The experience of France was somewhat similar but more aggravated. Apparently the years 1941 and 1942 were the worst, being marked by a decided increase in the more rapidly fatal forms of the disease. There was some improvement in 1943 and 1944.

In Greece and certain other countries in which malnutrition became extreme, there was unquestionably a marked increase in the mortality from tuberculosis but nothing more than this general statement can be made.

According to the Health Section of the League of Nations, the tuberculosis mortality of certain European cities increased markedly during Nazi occupation but has since declined. This is true of Paris, Brussels and Oslo. In other cities there was some increase during the occupation but this has been quite overshadowed by what has occurred since the cessation of hostilities. These cities include Amsterdam, Rome and Vienna. The German cities included

in the League report showed slightly increased mortality during hostilities but their subsequent history is not available.

Even neutral European countries did not escape. It is true that in Stockholm tuberculosis mortality continued on its downward course and this is apparently true also of that in Madrid, which is still on a very high level. In the 10 Swiss towns of more than 30,000 the rate remained more or less stationary although it had been declining before the War. The same is true of the incredibly high figures reported for Lisbon. And in Dublin mortality from tuberculosis increased almost 30 per cent from 1939 to 1942. It has fallen somewhat but in 1945 was still substantially above the prewar level.

An ethical reason may be added. Our scientific knowledge of tuberculosis is international in origin. A review is not necessary here, but it may be emphasized that if the great figures in the bacteriology and immunology of tuberculosis and in its diagnosis and treatment could be assembled they would constitute a truly cosmopolitan brigade. The discoveries of their genius are the rightful heritage of the entire human family.

The case for official international action against tuberculosis is thus extremely strong. Whether or not the World Health Organization will be enabled to take steps commensurate with the extent and seriousness of the problem is another question. The Draft Proposals do not specifically mention any disease but among the recommended functions there are included the stimulation and advancement of work to eradicate disease, particularly of an epidemic, endemic or social nature. In exercising these functions it is recommended that effective relationship should be established with non-governmental international organizations. By inference it is clear that those who drafted the proposals did not envisage an official agency which would be so comprehensive and well financed as to replace the voluntary agencies in various fields.

The recommended structure of the World Health Organization includes a Conference or Governing Body, an Executive Committee, Secretary General and Secretariat. Provision is made for the appointment of committees and commissions. The Conference and the Executive Committee would be exclusively governmental bodies. An Advisory Council might be set up but is not mandatory.

Under these circumstances it would seem clear that there is now and will be for many years a place for a strong non-governmental international tuberculosis agency. This agency should be world-wide in its membership. There is no valid reason for a voluntary agency to exclude neutrals and ex-enemy countries from membership. Reactivation and reorganization of the International Union would appear the simplest method of reaching this objective without undue delay.

Among the functions which a non-governmental agency might assume are the following:

1: The promotion of research. The Draft Proposals include promotion of research in the health field as a necessary function of the official organization. In tuberculosis the stimulation of research might largely be left to the Union. Most of the active

investigators throughout the world are members of their respective national associations.

2: The promotion of public education regarding the disease.

3: The establishment of diagnostic and other standards necessary for a world-wide tuberculosis program.

4: The exchange of information on all aspects of the problem.

Among the methods of carrying out such a program, emphasis should be placed upon the holding of international congresses. At the Washington Congress, 291 scientific papers were read. Also the general addresses and the exhibits did much to awaken public interest.

There is a well known example of stimulation of research resulting from an international congress. At London in 1901 Koch minimized the importance to man of infection with the bovine type of bacillus, stating that it must be of rare occurrence and of scarcely more importance than hereditary transmission. The Chairman, Lord Lister, immediately called attention to the defective character of the evidence which Koch had adduced, and questioned the accuracy of his statement. As a result Great Britain appointed a Royal Commission on tuberculosis which carried on fruitful research for nine years. Thorough investigations were undertaken also by Theobald Smith at Harvard, by Park in New York City and by various others in Denmark, France, Holland, Italy, Japan and Sweden.

A second method is by means of publications. Important articles should be made available in all the principal languages. An enlarged and revived Quarterly Bulletin, the publication of the Union, could do much in this direction.

A close relationship between the Union and the World Health Organization will be essential. The official Organization will have statistical services which should eventually assemble, refine and distribute data on morbidity and mortality from all countries. Presumably the Organization also will establish a library. For these and many other reasons the Union which now has its headquarters at Paris should give consideration to establishing itself at the site of the World Health Organization.

A word may be said regarding the financing of the Union. To carry out such a program as has been sketched it would be necessary to maintain a small headquarters staff and perhaps additional personnel for the field. Financial support will be necessary and might be obtained by having each national association designate for the Union a small percentage of its seal sale collection. Doctor Emerson has listed for me 55 countries which have issued Christmas seals for fund-raising purposes and in many of these the sale of these seals has become an annual practice. The double-barred cross was adopted as the international emblem of the campaign against tuberculosis at the Berlin Congress of 1902. If the plan of supporting the Union in this way were adopted, the emblem would become international in usefulness as it is in origin.

Tuberculosis then is an international problem, demanding international action for its solution. It is anticipated that the new World Health Organiza-

tion will have an active tuberculosis program. Also the Food and Agriculture Organization will promote the attainment of higher levels of nutrition. The International Labor Office is striving to improve hygienic conditions in industry. Adding together the probable programs of these official organizations and subtracting the total from what might be done internationally leaves a large balance of useful labor for a non-governmental agency specifically devoted to tuberculosis. Furthermore a strong non-governmental agency, such as the Union might become, could do much to obtain for official organizations the public support essential for their support and success.

SUMMARY

Plans are now under way to establish a new official international health organization to be called the World Health Organization. At the same time there is a proposal to reactivate the International Union Against Tuberculosis. It is timely, therefore, to discuss the urgency of international action in this field and the rôles which might be played by the official organization and by the Union, respectively.

Tuberculosis qualifies as an international problem for many reasons: (*1*) because of peculiarities in pathology and epidemiology, it has attained world-wide prevalence; (*2*) it constitutes a humanitarian problem of great magnitude, causing probably more than five million deaths annually; (*3*) it causes enormous economic loss; (*4*) it is affected by events beyond the control of any single nation, such as curtailment of food supplies, great epidemics of influenza and wars. Even neutral countries did not escape the influence of the second World War on tuberculosis mortality.

The case for official action against the disease is thus very strong. The World Health Organization, however, will be faced with a wide variety of urgent demands and, although its budget doubtless will be larger than that of any previous international health agency, it will be small in comparison with the needs.

It would seem clear that there will be a place for many years for a strong non-governmental international tuberculosis agency. Among its functions might be: (*1*) the promotion of research; (*2*) the promotion of public education; (*3*) the establishment of diagnostic and other standards; (*4*) the exchange of information on all aspects of the problem. Among the methods of carrying out such a program, the holding of international congresses is emphasized.

SUMARIO

Ya se han formulado planes para establecer una nueva organización internacional oficial de sanidad que se llamará Organización Mundial de la Salud. Al mismo tiempo hay una propuesta encaminada a revivir la Unión Internacional contra la Tuberculosis. Por lo tanto, resulta oportuno discutir la necesidad de la acción internacional en esta rama, y el papel respectivo que corresponde al organismo oficial y a la Unión.

La tuberculosis es problema internacional por muchas razones: (1) debido a peculiaridades patológicas y epidemiológicas ha alcanzado difusión mundial;

(2) constituye un problema humanitario de gran magnitud, ocasionando probablemente, más de cinco millones de muertes anuales; (3) provoca enormes pérdidas económicas; (4) la afectan acontecimientos fuera del dominio de ninguna nación aislada, como son la escasez de alimentos, las grandes epidemias de influenza, y las guerras. Ni los países neutrales evadieron el influjo de la II Guerra Mundial sobre la mortalidad tuberculosa.

Los argumentos en pro de la intervención oficial contra la enfermedad son, pues, poderosos. Sin embargo, la Organización Mundial de la Salud se verá confrontada con muchos y variados problemas, y aunque su presupuesto será sin duda, mayor que el de ninguna anterior organización internacional de sanidad, va a resultar pequeño en comparación con las necesidades.

Parece, pues, manifiesto, que por muchos años habrá lugar para un poderoso organismo internacional antituberculoso no-gubernamental cuyas funciones podrían comprender: (1) patrocinar la investigación; (2) fomentar la educación del público; (3) establecimiento de patrones de diagnóstico y de otro género; (4) intercambio de información relativa a todas las fases del problema. Entre los modos de llevar a cabo dicho plan recálcase la celebración de congresos internacionales.

THE TUBERCULOSIS EXPERIENCE OF THE UNITED STATES ARMY IN WORLD WAR II[1]

ESMOND R. LONG[2,3]

I am glad to have this opportunity to summarize the experience of our Army in handling its tuberculosis problem. But I look upon it as an opportunity, not so much for recapitulation, as for analysis and frank statement of shortcomings and imperfections in procedure that can be avoided, should the tragic necessity for mass mobilization ever arise again. Such an analysis is desirable, moreover, on other than military grounds at this time, for many of the procedures followed in the Army are of increasing applicability in civilian life.

Between Pearl Harbor and V-J Days the United States Government, through its various agencies, including the Selective Service System and the respective organizations of the Army and the Navy for voluntary enlistment, called up for physical examination, prior to acceptance for military service, more than 20 million men and women. The physical examination, in every case, included some form of medical scrutiny for detection of pulmonary tuberculosis. Fortunately the armed services had a proper respect for the menace of this disease. The experience of our own Army in World War I indicated clearly that tuberculosis can be a serious drawback to military effectiveness, increasing the so-called non-effective rate of military personnel, requiring large facilities for medical care, taking transportation needed for other purposes, utilizing the valuable time of Army and Navy doctors, and finally leading to high cost to the Government in compensation and other benefits for tuberculous veterans.

Knowing this, the Army and Navy made chest X-ray examination universal in the pre-induction examination of prospective troops as soon as it was practical to do so.

The story of induction has been told many times, and most of those interested in tuberculosis are now familiar with the induction station procedure and its results, the number of men rejected, and the saving to the Government through this method of detection and exclusion of tuberculosis. About 150,000 men and women with active or latent tuberculosis were rejected, with an early diagnosis made in thousands of cases, enabling prompt restoration to health and avoidance of further spread of tuberculosis.

My purpose here is to lay stress rather upon the imperfections of the procedure than its success. It should be emphasized first that the personnel assigned was never fully adequate for the job. The Army maintained approximately 100 induction stations, which varied in their load from 100 to

[1] Presented before the Joint Session of the Medical and Public Health Sections at the 42nd annual meeting of the National Tuberculosis Association, Buffalo, New York, June 13, 1946.

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3,000 examinations a day. A one-hundred man station could operate with one roentgenologist, while a station examining 3,000 men needed 8 or 10 roentgenologists a day. These figures are based upon the principle that 300 examinations constitute an optimum load. As it worked out, however, not infrequently one radiologist examined a thousand films a day. Such loads are not intolerable for two or three days, but efficiency drops notably when they are maintained for weeks at a time. The personnel employed consisted of both civilian and Army roentgenologists. Men of outstanding reputation were included, but their number was relatively small. Many of the civilians were elderly, and unfamiliar with the diagnosis of minimal tuberculosis. Most of the military personnel, on the other hand, were youthful, but often they were insufficiently trained in diagnostic methods. The majority of military personnel had had the advantage of training in the Army School of Roentgenology, but their responsibility was heavy and their training was too brief.

All honor, however, to the men who manned the X-ray units of the induction stations! They met a ceaseless stream of inductees and handled it not too badly. It is no wonder that their judgment was at times made subservient to rule of thumb procedure. Instructions were drawn carefully to aid them in making quick decisions. In retrospect it is easy to see that their attention was focused too sharply on the mechanical standards established by Army regulations, and not infrequently drawn away from small infiltrative lesions that would have been considered of the utmost significance by competent phthisiologists with sufficient time for the exercise of judgement. I refer particularly to the undue emphasis upon large and numerous calcified nodules of healed tuberculosis and failure to recognize the small "soft" shadows of minimal fresh apical tuberculosis. It is known, through sampling done by the Office of The Surgeon General during the war, and through comparison of induction and discharge films of men breaking down, that several thousand small infiltrative lesions were overlooked by the induction station roentgenologists in the millions of films examined. But it is a fair estimate that 90 per cent of the significant lesions that should have been seen were discovered.

Such oversights should never occur in such number again. The best insurance against their recurrence is a well-trained, stable personnel, experienced in the detection of tuberculosis, and on duty in sufficient number so that no man is expected to carry a load of more than 300 films a day over prolonged periods of time. From the point of view of administrative efficiency, I believe this personnel should be military, not civilian. This is said with due recognition of the splendid work done by many civilian roentgenologists in induction stations. It would be preferable, however, to hold young officers in Army training stations longer and then keep them on the job. This proposal would, admittedly, meet two serious difficulties. First, the work is extraordinarily monotonous, and few radiologists would care to devote years to it in a prolonged conflict like the last. Second, such a proposal would meet intense resistance from other elements of the Medical Department of the Army, for in wartime the number of hospitals to be staffed is large and, in periods of increasing military

activity, the pressure for more personnel is constant and urgent. Substitution of tuberculosis experts trained in reading chest films only, as from time to time suggested, would not solve the problem. Chest lesions of incredible variety are seen in induction stations, and one-fifth of the films taken are of other parts than the chest.

DIAGNOSIS AND CARE OF TUBERCULOUS PATIENTS IN THE ARMY

The diagnosis and care of tuberculosis in the Army were highly creditable. The great difficulty of the induction stations, excessive speed of operation, was far less in evidence in Army hospitals. Not only in the large general hospitals, but in every station hospital, more time was available for clinical and laboratory study. The cases of tuberculosis that escaped detection at induction stations were found in high proportion within a relatively short time by the medical personnel of Army posts. It will not be surprising to learn that only a minority of these were discovered on the basis of symptoms. Advanced cases came to the attention of medical officers in this way, but, fortunately, there was an immense amount of routine examination, as for Officer Candidate School or for special service, in which X-ray examination was incorporated and in which the opportunity for the discovery of early tuberculosis was again afforded. In general the approach in treatment of these cases was conservative. More cases of inactive than of active minimal tuberculosis were held under observation.

Most of this audience is fairly familiar with the system of Army hospital care in the continental United States. Inducted troops were widely dispersed for their basic training over hundreds of Army posts throughout the country. Each of these posts had its station hospital. Practically all of the tuberculosis cases discovered in this country were found on these posts. Following observation and initial care in station hospitals, disposition was effected by one of three routes. Cases judged nontuberculous, after appropriate observation, and cases judged clearly inactive, were returned to duty. Cases of clearly active tuberculosis in enlisted men below the first three grades of non-commissioned officers were discharged to the Veterans' Administration. In accordance with an established Army provision for retention in the Army of personnel in which considerable investment had already been made and in which special qualifications had been found, men in the top three grades of enlisted personnel, and commissioned officers were sent to special tuberculosis centres in general hospitals. Cases needing special study were likewise transferred there. At first there was only one of these, Fitzsimons General Hospital near Denver, Colorado. Later, when the load of new cases became too large for Fitzsimons General Hospital, two other hospitals were made centres for tuberculosis, Bruns General Hospital near Santa Fe, New Mexico, and Moore General Hospital near Asheville, North Carolina. Each of these was a general hospital, in which tuberculosis was one of a number of specialities. The peak load in these hospitals, which has been passed only in recent months, was about 3,500 tuberculous patients. The total number of patients admitted in all hospitals for study with respect to tuber-

culosis, was about 25,000. In four years approximately 16,000 men were discharged because they had active disease. This number constituted about one-sixtieth of all medical discharges from the Army.

The care given in these hospitals, in spite of all statements that may be made to the contrary, was of high order. Only one familiar with the intense competition for personnel and the inevitable turnover of personnel necessary in the maintenance of a fighting force overseas, can appreciate the difficulties in operation of wards requiring the long-term care necessary for tuberculosis. Many an officer with high ideals in the treatment of tuberculosis, deeply ingrained by his training, was profoundly depressed by the obstacles he encountered in these hospitals. It is a noteworthy fact, however, for which I can can vouch by repeated personal observation, that many of these officers now feel that the care was superior to that in many of the well known institutions for the care of tuberculosis to which they have returned.

Soldiers' complaints about the food, lack of nursing attention, failure to see their physicians as often as they wished and insufficient diversional and recreational facilities, are familiar in civilian hospitals. No one ever worked harder than the personnel of the three hospitals I have named to overcome these difficulties and to give our tuberculous soldiers the best medical care available.

That care was spectacular in no way. Standard methods were used. Chiefs of service were men of experience in either civilian life or the Regular Army. Every Army hospital was a training post. Every Army hospital had to furnish men for oversea service. In so far as possible staffs were made up of men with some experience in tuberculosis. But many of the officers on duty had not specialized previously. Young men scarcely out of medical schools came in for training and indoctrination, and often were transferred to oversea units as soon as they became skilled, to be replaced by other new officers recently taken into the service. Repeatedly I have seen these young men in staff conferences, shortly after their arrival, hesitant and inexperienced, and observed them six months later, already veterans in their understanding of the care of tuberculosis.

It is not easy to outline a suitable program for handling tuberculous patients if a comparable necessity should arise again. It cannot be done, in any event, without a brief analysis of the system of Veterans hospitals. In theory, and correctly in my opinion, the Army does not consider the long-range care of tuberculosis a proper responsibility of the Army Medical Corps. Tuberculosis requires long treatment, and, as far as possible, that care should not be broken up. It should proceed in an orderly manner in one sanatorium, with proper convalescent follow-up and modern rehabilitation measures. The system of Veterans' hospitals has been set up for this purpose. The principal function of an Army hospital is to restore soldiers to effective duty as members of the Army. Whatever moral obligations may appear involved in the care of men who have been wounded or broken down in military service and can no longer serve effectively in the capacity for which they were taken into the Army, it

is a practical fact that the volume of short-term care patients in the Army is so large, and the opportunity to turn men back to service likewise so great, that it is a misuse of Army hospital space to hold long-term cases indefinitely.

Consequently there should be a first class Veterans organization for taking care of long-term cases. It is general knowledge that such a system was not in operation in time to care for the chronic cases of this war. This holds for all chronic illnesses, not for tuberculosis alone. The Army has held thousands of cases, including cases of tuberculosis, that should have gone to the Veterans' Administration long ago, and would have gone had space been available. This statement is in no sense a criticism of the Veterans' Administration, which is making a truly magnificient effort to provide the necessary facilities. It is an inescapable fact, however, that, under the restrictions prevailing, with personnel and construction priorities set as they were, the Veteran' Administration was not in a position to establish hospitals on the scale required for hospitalization of the chronic illness that might be expected from a total force of 15,000,000 service men and women.

Were the job to be done over again the following system would appear appropriate:

(1) Periodic, routine surveys of Army personnel to discover cases in their incipiency. This is a mammoth task, and of almost indescribable difficulty in an active theater, but not too difficult for accomplishment, with the improved radiological equipment now available, in troops in service in this country. Such a system is indeed in prospect for the peacetime army.

(2) Establishment of one centre for tuberculosis in each service command or comparable area, to which cases discovered on Army posts and in routine surveys could be sent. Each of these centres should be staffed by men experienced in the diagnosis and care of chronic chest diseases.

(3) Comparable provision for officers and all grades of enlisted men. The whole question of Army organization is outside the scope of this paper, and I have no intention of going into it here. From both administrative and professional points of view, however, it is more practical to treat tuberculosis as a purely medical problem and dispose of cases in the same way.

(4) Early discharge to the Veterans Administration. Under this plan the Army centres would be established only for proper initial care for tuberculosis, not for long-term care. The latter would be assumed by the Veterans Administration, which should have personnel in adequate number, and of capacity not inferior to that in any of the tuberculosis institutions in the country. Hospital facilities and the number of beds available should be fully adequate.

Such a system, in my opinion, would be an orderly one, and superior to the present, which is an outgrowth of necessity.

DISPOSITION OF PATIENTS WITH TUBERCULOSIS

I have anticipated this in the preceding section. On the whole, the problem of proper disposition was well handled It is an exceedingly difficult one at best. It is based upon the fact that a man with active tuberculosis is incapacitated for military service. Just as a man with active tuberculosis must be

rejected prior to induction, so a man discovered with this disease in the Army must be considered unable to serve, and hence considered for early discharge. This disposition, obviously, overlooks the possibility that a man may be cured. However, medical judgment recognizes that rapid permanent cure is not possible, and that clinical arrest of the disease is very different from cure. Disposition must be based upon the fact, also, that under prevailing circumstances, a man can rarely be held in an Army mobilized for an emergency until he can be pronounced cured, and that a soldier with apparently arrested disease may soon break down again. It is obviously different in the Regular Army, where Army service is a lifelong career. But under wartime circumstances, there is no argument with the fact that patients with moderately and far advanced tuberculosis must be considered from the Army point of view as permanently incapacitated. Moreover, unless an emergency is expected to endure for several years, the same holds true for most cases of active minimal tuberculosis. However, it appears a mistake to say that every case of minimal active tuberculosis should be discharged as permanently incapacitated A similar, but still more difficult problem, exists in the case of pleurisy with effusion. Most patients with pleural effusion make apparent recovery within a few weeks. Yet long experience has shown that not a few break down in later years. Nonpulmonary tuberculosis susceptible to surgical treatment offers a similar problem. Cure might be prompt, and yet be difficult to establish beyond doubt. Policy with respect to the disposition of cases of minimal tuberculosis, pleurisy with effusion and certain forms of nonpulmonary tuberculosis, is still in a state of flux. It is probably true that many patients have been returned to duty who should have been considered incapacitated and discharged. It is probably true, also, that not a few patients have been discharged as incapacitated, when a few months more of care and properly regulated service subsequently, would have permitted cure and continued military performance. In the brief space permitted by this paper I shall not attempt to outline a procedure that might be equitable in the disposition of all such cases. I would only call attention to a recent proposal, still under consideration, that the system employed by the Veterans' Administration in rating disability be adopted as appropriate for such cases. This permits initial generous estimate of disability, with periodic subsequent review to determine ability for performance and permit readjudication of pension. The safest procedure would be to discharge from the Army all non-regular military personnel who have been discovered to have active tuberculosis, provided they could be assured adequate continuing care under Veterans' Administration auspices, and provided also that suitable adjustment of pensions were made so that proper compensation was in effect when needed, but not, on the other hand, continued indefinitely, as is the case at present with many well arrested cases of tuberculosis in both officers and enlisted men.

EVACUATION OF TUBERCULOUS PATIENTS FROM OVERSEAS

Cases of tuberculosis were discovered in oversea units in the same manner as in the continental United States, that is, on the basis of symptoms, and in the course of various routine examinations and examinations for other purposes.

Many were discovered by chest X-ray studies of men with acute respiratory disease. There is less opportunity for temporizing overseas than in this country, so that not only all active cases, but many doubtful cases should be returned to the United States for proper study and care. This procedure was generally followed in all of the theaters. Evacuation was subject to many difficulties in the early days of the war. Hospital ships were not sufficiently numerous, and air evacuation had not been developed. Most tuberculous patients in the early months came home, troop class, on transports. From a public health point of view this was objectionable, for little isolation was possible, and the care that should be given active cases was ordinarily not possible on transports.

Later this situation was in large measure corrected. Hospital ships were increased in number and airplane evacuation of tuberculous patients became common. The accommodations for tuberculous patients were first-class. All hospital ships had quarters for contagious cases. Frequently the only communicable disease on board was tuberculosis. It was found that only a few rooms needed to be reserved for the usual acute contagious diseases, and this section frequently was turned over to tuberculosis. Quarters were airy and cheerful, and patients enjoyed the trip. Pneumothorax was given when necessary on such ships, and in general no untoward developments resulted.

Airplane evacuation also was remarkably effective and will undoubtedly play a larger part in the future. Patients held for weeks in Army hospitals, perhaps after years of service overseas, were carried aboard big transport planes on litters and twenty-four hours later were in comfortable hospitals in the United States. After a few days of rest in the debarkation hospitals, many were again carried by plane, in a few hours, to one of the big hospital centres. It would seem that, in the future, evacuation of tuberculous patients should be a problem easily handled.

SEPARATION PROCEDURE

Every examination for separation from service included special study for tuberculosis. Army regulations since the beginning of the war have required a chest X-ray examination prior to discharge. In a relatively small number of cases in the early months this requirement was overlooked, so that it is not a fact that every man who served has had such an examination. Within the last three years of the war, however, with rare exceptions, every man discharged had the required X-ray study. This examination, it must be admitted, has been beset by all of the difficulties that were so serious in induction stations. In some respects these were encountered in exaggerated form. The war lasted so long that, in all fairness, the trained men with long service had to be discharged before the medical job of separation was finished. Consequently the personnel of separation centres ultimately consisted in large part of young officers insufficiently trained. When the separation centres were first organized, the roentgenologists on duty were men who had had experience in induction stations, or radiological experience in Army hospitals here or overseas, or were graduates of the Army School of Roentgenology. A time came when a con-

siderable proportion had their principal training on the job. Inevitably numerous errors of omission have been made. It is no secret to this audience that not a few cases of tuberculosis that should have been easily detected, were missed at separation centres. The speed of separation was so great, the original training of the radiologists assigned, in many cases, so short and, above all, the turnover of personnel so frequent as to interfere seriously with the proper operation of a separation centre. Only one who has seen the long trains of troops arriving from ports of debarkation and who knows the personnel shortages that existed not only in the professional field, but in every type of labor in the separation centres, can appreciate the enormous difficulties in performing a creditable piece of professional work. Nevertheless, the total job, if not beyond reproach, was highly successful, and one reflecting great credit upon the Medical Department of the Army. Several thousand cases of tuberculosis which had escaped detection on induction or developed from unrecognized lesions or from fresh infections within the Army were discovered at these centres. The great majority of these had minimal tuberculosis. The early diagnosis and care given these men have saved many lives, and the discovery and immediate hospitalization of men with positive sputum has been of inestimable value to the long-range public health program of the nation. The separation centre X-ray examination for tuberculosis, with all its imperfections, was a public health procedure of the first order.

TUBERCULOSIS MORTALITY

Before closing I should like to call attention to the Army of the United States as a population group with a uniquely low tuberculosis mortality. Combined figures from the Office of The Surgeon General and the Veterans Administration, representing the tuperculosis mortality of the entire Army group, including its discharged members, are now available. This group is one of peculiar significance, for it is a screened population—screened with the imperfections I have described in this paper—but nevertheless one from which the majority of tuberculosis cases were removed.

This group, consisting of approximately 4 million men in 1942 and increasing to more than 11 million in 1945 had an average tuberculosis mortality of less than 4 per 100,000 per year in 1942. The mortality increased to about 6 per 100,000 per year in 1943 and to 10 in 1944. A slight rise was again evident in 1945, the last period for which figures are available, when the average mortality for members of the existing Army and discharged men and women who had served in the Army from 1942–1945 increased to 12 per 100,000 per year.

During this time the gross mortality rate for males of corresponding age in the United States fluctuated slightly, but remained fairly constant at approximately 52 per 100,000 population per year.

The phenomenon observed is of great epidemiological importance. A group with a relatively low tuberculosis mortality rate at the start, but with a certain percentage of unrecognized cases in its midst, has shown a significant rise in its rate within the period of four years, at a time when the mortality rate of the population from which it was drawn has remained practically constant.

It is too early, at the present time, to do more than call attention to the phenomenon in question. Intensive research will be required to evaluate such factors as exposure to contagion in the United States and overseas, and assess the rôle played by endogenous reinfection in the time-period involved. It will be of very great interest to follow this population in the years to come. A cumulative rise in the incidence of infection, with a corresponding mortality, may be expected. On the other hand, this population is returning to an environment of lessening incidence of infection, as judged by general mortality figures, and it may be anticipated that, with proper care of the veterans who have already contracted tuberculosis, the mortality will drop, and always remain well below the level of the population of corresponding age without military service. Time alone will make it possible to answer this question.

SUMMARY

In this paper I have not tried to recapitulate, in detail, the measures used by the Medical Department of the Army in controlling tuberculosis, or to discuss their degree of success in the light of the experience of other armies or military services. This has been done before, and it is perhaps enough to say here that the incidence of tuberculosis was the lowest in the history of the Army, and far lower than in our Army in the first world war, in which the problem was somewhat comparable, but it should be recognized at the same time that the recent period was more favorable and the means for control much more effective than during any previous period.

Rather, in this paper, I have attempted to place on record, for the sake of the future, a summary of the deficiencies in the program of the Army, calling attention to facts perhaps not generally known that prevented that measure of success which might have been expected in a stable civilian population in peacetime. It must be recognized with all sympathy that certain shortcomings were inevitable in a program that had to be integrated with every other phase of the operations of the Medical Department of the Army. This integration, in the interest of a balanced medical service, meant far less than optimum coverage for tuberculosis control—in manpower, available time and facilities, but above all in personnel professionally trained for the responsibility assigned.

In retrospect it is clear that many improvements could have been made, and it is hoped that these will be incorporated in the program of the future In spite of its defects, however, the program was a notable one in case-finding and treatment, saving many lives through early diagnosis, and preventing much further spread of disease by isolation and treatment of sources of contagion. In that achievement the personnel of the induction stations, dispensaries, medical field installations, Army hospitals and separation centres have been a highly effective force in the general antituberculosis campaign of the country.

SUMARIO

En este trabajo no se trata de recapitular con todo pormenor las medidas utilizadas por el Departamento Médico del Ejército de los E. U. A. para co-

hibir la tuberculosis, ni tampoco de discutir su mayor o menor éxito a la luz de lo logrado en otros ejércitos o servicios militares. Ya se ha hecho esto antes, y quizás baste con decir aquí que la incidencia de la tuberculosis fué la más baja en la historia del Ejército de los E. U. A. y mucho menor que en nuestro Ejército en la I Guerra Mundial, en la que el problema era algo comparable, aunque también debe reconocerse que el período reciente fué más propicio y los medios de lucha mucho más eficaces que durante cualquier período anterior.

Trátase más bien ahora de sumarizar para el futuro las deficiencias de que adoleció el plan del Ejército, llamando la atención sobre ciertos hechos quizás no muy bien conocidos que impidieron conseguir el éxito que hubiera sido de esperar en una población civil estable en tiempos de paz. Hay que reconocer con toda consideración que ciertas fallas eran inevitables en una obra que tenía que integrarse con todas las demás fases de las operaciones del Departamento Médico-Militar. Esa integración, con su propósito de equilibrar los servicios médicos, tuvo por resultado una atención muy inferior a la óptima, en cuanto a lucha antituberculosa: en personal, y tiempo y medios disponibles, pero sobre todo en personal profesionalmente adiestrado para la tarea que le incumbía.

Retrospectivamente, parece manifiesto que hubieran podido hacerse muchas mejoras, y se espera que las mismas formen parte de las obras del futuro. Sin embargo, aun con todos sus defectos, el programa fué notable en lo relativo a descubrimiento y tratamiento de casos, salvando muchas vidas mediante el diagnóstico temprano, e impidiendo mucha propagación ulterior de la enfermedad, mediante el aislamiento y tratamiento de los focos de contagio. En esa realización el personal de los puestos de reclutamiento, los dispensarios, las instalaciones médicas en campaña, los hospitales militares y los centros de separación han constituído una fuerza sumamente eficaz en la campaña antituberculosa en general del país.

THE SIGNIFICANCE OF REHABILITATION[1]

ERNEST S. MARIETTE[2]

It is short-sighted to spend a great deal of time and money in developing an excellent medical program for the treatment of tuberculous patients without at the same time providing some form of supervised activity for patients with a favorable prognosis to enable them to bridge the gap between the sheltered life in a sanatorium and the life of the work-a-day world.

The total number of hours which are to be filled during the months of sanatorium stay are many. The patients have no definite responsibilities, no engagements to keep, nothing to do except get well. The manner in which the sanatorium decides that these hours of cure-taking shall be spent may have as great an influence upon the future emotional, mental and economic life of the individual as the method of treating that person will have on his physical life.

Because of the nature of tuberculosis, patients will tend to drift into those occupations which require mental rather than physical effort. They also may be forced to reduce their hours of occupational activity and increase their hours of leisure. If the sanatorium program has been properly planned and carried out, the patients will leave the hospital with their physical handicap compensated to a certain degree by mental training and with correct ideas on how to spend their hours of leisure.

For the purpose of discussion, we will divide the selection of patients for rehabilitation into two groups: (*1*) in-patients and (*2*) ex-patients.

Rehabilitation for in-patients: The medical criteria for the selection of patients for rehabilitation will depend on how the program in the sanatorium is organized. We believe any person with a favorable prognosis is entitled to be considered for some type of rehabilitation. This should be begun as soon as the patient's condition has improved sufficiently for him to read or do some occupational therapy work in bed. Certainly he can spend his time in this way without any more harm to himself than when he reads pulp magazines or plays cards.

On the other hand, the patient with a poor prognosis is not entitled to a definite rehabilitation program. However, the librarian can help him select the proper reading suited to his mentality or the occupational therapist can provide a type of activity which suits his manual dexterity and satisfies him mentally. The physician can recommend some type of rehabilitation training when his prognosis changes.

Therefore, in our opinion, just when the in-patient is ready to begin rehabilitation depends upon how the program is organized in the sanatorium and the judgment of his physician.

A detailed study of the patient must be made in order to avoid wastage of time

[1] Presented before the Medical Section, as part of a symposium on *Medical Management of the Recovery Phases of Tuberculosis*, at the 42nd annual meeting of the National Tuberculosis Association, Buffalo, New York, June 12, 1946.

[2] Medical Director and Superintendent, Glen Lake Sanatorium, Oak Terrace, Minnesota.

and money in retraining a person who is hopelessly ill and has no chance of recovery, or in retraining some patient in an occupation which he is not capable of carrying on. In 1929 we set up the following mechanism to accomplish this. The Admitting Department notifies the Education Department of the admission of each patient. After the initial study of the patient and the determination of his prognosis, the physician is approached to ascertain when the patient will be well enough for some activity which can be carried on in bed. The Education Department then proceeds to learn what it can about the patient's educational background. The Social Service Department also secures detailed information concerning his previous work record. The State Division of Rehabilitation gives the patient a battery of standard vocational tests whenever indicated.

After all of this information has been obtained, the patient's problem is referred for recommendations to a committee consisting of representatives from the Social Service, the Education, the Rehabilitation and Occupational Therapy departments, the Library and the physician. Before the recommended plan is put into operation, it is discussed with the patient so that he feels he has had a part in making it and from that time on his life in the Sanatorium has a purpose. He is now working towards a definite goal and, even though he starts just with selected reading, he knows that as his condition improves the time will come when he will be allowed to go to the classroom for group instruction.

The length of stay in Glen Lake Sanatorium varies between thirteen and fifteen months, and as we attempt to keep patients until they have completed four hours of exercise per day for four months, they have ample opportunity for a good start on a prevocational program.

Rehabilitation of ex-patients: The medical standards for the selection of ex-patients for post-sanatorium training will depend largely on whether it will be carried on in the regular industrial channels or in a sheltered environment such as the settlement colonies in England or some workshop such as the Altro Shop in New York.

Wherever it is carried on, the responsibility for the post-sanatorium training lies with the State Division of Vocational Rehabilitation or some similar agency. This Division attempts, at state and federal expense, to retrain the ex-patient in accordance with the terms and conditions of the Barden-La Follette Act with the approval of his physician. In doing this it pays his tuition in a regular training school or in industry, whichever seems to fit in best with the individual needs of the patient.

If the vocational counselor has made contact with the patient while he is still in the hospital, as is done at Glen Lake Sanatorium, said patient's pre-vocational training will have been directed along the lines which will fit into his post-sanatorium program. Most communities do not have a sheltered workshop, so the patients will have to be retrained in the regular industrial channels. Under these conditions careful selection of patients for training is necessary. For instance, our agreement with a local trade school was nearly cancelled when the school discovered that one of the trainees recommended for training by his private physician had tubercle bacilli in his sputum. Industry cannot be expected to

open its ranks to such ex-patients unless perchance a special department has been established for them which is acceptable in all particulars to the established health authorities.

Patients selected for training through the regular industrial channels should, as a minimum, meet the requirements of an arrested case of tuberculosis, as defined by the National Tuberculosis Association. The trainee's chances for successful rehabilitation will be enhanced if in addition to these standards the sputum has been negative and the lesion stabilized for at least nine months or a year and his exercise period has been increased to that adopted by us or longer before the post-sanatorium program is begun.

The same strict requirements will not be necessary if the rehabilitation is to be carried out in some type of sheltered employment whether it be in a settlement colony as in England or in a workshop such as the Altro Shop in New York. This shop divides its trainees into three broad groups:

Group 1 includes those patients with an absorbed pleurisy or an early lesion whose sputum was never positive while in the sanatorium and who became stabilized on bed-rest alone, so that they had a rather even course in the sanatorium. Perhaps we can say that the patients in this group constitute the minimal favorable cases. They should require about a year of training.

Group 2 includes those who needed to have bed-rest supplemented by collapse therapy, who had a moderately severe course while in the sanatorium, but whose sputum was converted from positive to negative before discharge. They should require about one to two and one-half years of training. The patients in that group might be considered to comprise the moderately advanced group whose prognosis is favorable. In my opinion, groups 1 and 2, provided they have had a sufficiently long hardening-up process while in the sanatorium, could receive post-sanatorium training in the regular industrial channels just as well as in the sheltered workshop. If that is done, suitable safeguards should be set up to correct the difficulties inherent in such a program.

Group 3 includes patients who had a rather stormy course while in the sanatorium, whose pulmonary reserve is low, whose sputum is still positive, but who are capable of some type of work. They would be considered as good chronics and will fall into that group of people who must live with their tuberculosis and, therefore, must keep their activities below the fatigue level. This group is not suitable for training in the regular industrial channels because the possibility of relapse is too great and because they are potential health hazards for the other trainees as well as the training faculty. However, they might be suitable for some form of sheltered employment.

This group should be subdivided into (*a*) those who have to live with others in a boarding house or elsewhere. They should remain in the sanatorium until their sputum has become negative. (*b*) Those who have a home in which there are no young children. If they will follow the suggestions of the health department, they should be permitted to go to their homes under supervision of that agency. They may be able to carry on some occupation in the home but this is usually not particularly satisfactory.

This group should not receive post-sanatorium industrial training unless it can be carried on in some form of sheltered employment. Tuberculosis is an infectious disease and if we cannot render the ex-patient safe to associate with other members of society without harm to them, he should not be permitted to do so.

What are the relapse dangers in post-sanatorium training or employment? The success of any post-sanatorium program is enhanced if the patient is followed by a periodic check-up including a chest X-ray film and sputum examinations. These check-ups should be carried on by someone who understands the chronic nature of tuberculosis with its tendency to relapse and who will therefore be alert to any change in the patient's symptoms or findings.

The periodic check-up should be repeated every three months during the first year, every six months during the second year and annually thereafter. Perhaps one might conclude that the training in a sheltered workshop or in the regular industrial channels had been successful if the X-ray film at the end of the training period showed no change from that at the beginning, except a further increase in fibrosis. The sputum should be consistently negative to all tests during the training period.

The program itself should not involve long hours, heavy work or undue strain, and extra rest should be provided in the beginning. Some companies have solved this by limiting such employees to an eight hour day schedule for five days a week, preferably on the first shift. Overtime is not permitted in the beginning and a two-hour rest period following work is strongly emphasized at the start. In some instances employment is started on a part-time basis and, as the patient's strength and condition permit, gradually increased to a full day's employment.

The sheltered workshop, on the other hand, may permit persons with positive sputum to be trained on a part-time basis with a regular rest period. In that way many of the so-called good chronics can be made partially self-supporting without harm to others.

If fact, any well coördinated or well planned rehabilitation program will convert many a discharged patient from a public relief recipient to an industrially occupied man, in many instances at a higher salary than he received prior to his illness. If to that one also adds the mental contentment and the restoration of self-respect and the joy and zest of life which goes with economic security, we have a program which is really worth while and which cannot be measured by any entry in the financial ledger.

Foster in a study of over 400 rehabilitated patients who were reviewed four years after discharge found that only 12 per cent of them were dead or had their disease reactivated in contrast to 48 per cent who had died or had their disease reactivated out of 6,906 ex-patients where rehabilitation had not been used.

The Altro Shop reports that where the persons had received three months of retraining, and irrespective of whether or not they were able to complete their full training period, 62 per cent were able to work or working on the tenth anniversary of their discharge. Truly a wonderful record. If, however, one

considers only those who were able to complete their full training program, the Altro Shop reports that 85 per cent were able to work or working on the tenth anniversary after their discharge.

Carlson and Dabelstein of Minnesota analyzed the status of 322 discharged sanatorium patients who were given some type of vocational training in a period from July 15, 1935 to May 15, 1939 and found that 63 per cent of the total group were able to engage in full time work, 17 per cent were able to work part time, while only 20 per cent were unable to work at the time the study was made. In the four years from 1939 to 1943 a total of 47 ex-patients have lived in the Sarahurst Boarding Club while receiving training. This group is small but still the results are very interesting. Of the 47 boarding club patients, 91.5 per cent were well and working and 8.5 per cent have had relapses.

While varying conditions in different communities may call for different types of plans, the above record indicates that a well prepared and well carried out rehabilitation program, whether it centers about a sheltered workshop or an attempt to ease the ex-patient into the regular industrial channels with a very careful medical follow-up including periodic check-ups, offers the ex-patient an excellent chance of remaining well and living a happy and useful life.

REHABILITATION OF THE TUBERCULOUS[1]

The Program of a Municipal Sanatorium

I. D. BOBROWITZ[2]

A detailed description of the Otisville rehabilitation program is soon to be published by the National Tuberculosis Association. I would like, at this time, to outline some of the main features of our work and to present some of our experiences.

A complete rehabilitation process involves not alone the period in the sanatorium, but also the time before admission and after discharge. Our program can, therefore, be divided into three intimately related phases which are of equal importance—the pre-sanatorium, in-sanatorium and post-sanatorium periods.

From the time of diagnosis and thereafter, public and voluntary agencies, such as medical, welfare, social service and public health nursing, work with the patient and family and refer the patients to the sanatorium. These are known as the referring or active working agencies. Rehabilitation groups come into the picture during and after the sanatorium period. The functions, responsibilities and relationships ascribed to these organizations had been agreed upon after a series of meetings attended by the sanatorium and the agencies.

PRE-SANATORIUM PHASE

It is unwise to expect a patient to contentedly accept hospitalization unless home circumstances are satisfactory. Consequently prior to admission, the referring agency examines the entire family situation and attends to disturbing social, economic or health problems. It is also necessary to prepare the patient and family for institutional care and the referring agency outlines the general features of the sanatorium and post-discharge period. A good personal approach at this time can create understanding of the illness and build up confidence and optimism. The patient is also provided with a pamphlet describing the Sanatorium. These pamphlets were prepared by us, and in them all of the departments and services are explained. Thus the patient can get an idea of what the institution is like and what can be done to help him.

IN-SANATORIUM PHASE

On admission we request essential personal, social and family information in the case. These important details are available from the referring agency from previous home visits and frequent contact with the patient and family. With this knowledge we can better understand the patient and his home situation and more

[1] Presented before the Medical Section, as part of a symposium on *Medical Management of the Recovery Phases of Tuberculosis*, at the 42nd annual meeting of the National Tuberculosis Association, Buffalo, New York, June 12, 1946.

[2] Medical Superintendent, Municipal Sanatorium, Otisville, New York (one of the institutions of the Department of Hospitals, City of New York).

easily and intelligently determine his needs. Because of the relationship that exists between the Sanatorium and the community organizations, it is possible to solve various home problems that may arise while the patient is in the institution, such as welfare assistance, intensive case-work or medical care for the family. Immediate reports can also be obtained by us for home information requested by the patient.

After admission the patients have five illustrated lectures which ready them for sanatorium care and give them basic information about tuberculosis. One of the talks is devoted to rehabilitation, and from it, the patient can learn what rehabilitation is, how it works and the benefits he can derive from it. Patients who understand the program readily accept it. There are, in addition, numerous opportunities for education from the contact of the patient with the Sanatorium rehabilitation personnel.

To organize and apply successfully a sanatorium rehabilitation program, a complete educational scheme is advisable for the employees and the medical staff. This will help to obtain their interest, coöperation and understanding.

The patient's work tolerance is based upon the accepted criteria for activity of his tuberculosis, that is, symptoms, sputum findings and the roentgenological appearance of the lesion. Prognosis, treatment and complications are also considered.

Infirmary and semi-infirmary patients have no regular rehabilitation assignments, but special reading, self-study or bed-side instruction in school subjects may be planned. The patients must be in an ambulatory ward for at least one month before participation in the program. The minimum criteria for rehabilitation placement are as follows: No symptoms; sputa, gastrics and cultures negative for at least three consecutive months, roentgenograms stable for the same period; no contraindicating complications; collapse therapy effective with a minimum of three months after initiation of pneumothorax, and six months after thoracoplasty. In other words, when assigned, our patients fulfil the criteria of the N. T. A. for an apparent arrest of the disease, except that some have not had a daily exercise allowance for two months.

Most patients meet more than the minimum requirements outlined. It must be emphasized that assignments to rehabilitation are not determined merely by the stage of the disease or type of therapy. Any patient who has made good progress and who satisfies the strict medical criteria for placement can be safely rehabilitated.

Our patients are in a good prognostic group, with about 45 per cent minimal, 45 per cent moderately advanced, 5 per cent far advanced, and 5 per cent with pleural effusion or glandular tuberculosis. From 35 to 40 per cent undergo collapse therapy.

The initial allowance for rehabilitation is one hour daily. As the patient's condition improves, the work tolerance is gradually increased, usually at the rate of one hour a month. During 1943 to 1945 inclusive, 945 patients were discharged with rehabilitation service. These patients had more than three months (actually an average of 102 days) in the rehabilitation program. Their

daily work tolerance on discharge was as follows: One to two hours, 18 per cent, (many of these were patients who left against advice); three hours, 16 per cent; four hours, 61 per cent, and five to eight hours, 5 per cent (the physical activity of this last group was increased so that the patients could accept employment in the sanatorium or on the outside). The point to be made is that a satisfactory work tolerance is achieved by the patients and they are in rehabilitation for a sufficient time to derive benefit from it. The purpose of the assignment can be accomplished and they can be made ready for referral to outside rehabilitation centres.

Careful medical control of rehabilitation is essential and patients must be deliberately selected and carefully supervised. With adequate medical guidance constantly provided, rehabilitation is a safe form of therapy. Primary consideration is always given the medical or surgical needs of treatment. During the past three years 1,006 patients entered or were assigned to the program and 79, or 7.8 per cent, were removed for reasons associated with their tuberculosis. Many of these patients were eventually reassigned.

There is a Sanatorium team responsible for the patients' rehabilitation. The Medical Director or Superintendent has the over all direction of the program and the minimum number of people required to work with him include the rehabilitation counselor, resident physician, occupational therapist, nurse and medical social worker. There may be, in addition, teachers for academic and business courses and other Sanatorium personnel to help in training or teaching the patients.

No patient is assigned to the program without a group opinion arrived at by presentation and full discussion at a rehabilitation case conference. This session is attended by the Sanatorium team, with the Medical Superintendent as chairman. The preparation for the conference follows a special pattern. The rehabilitation counselor procures pertinent information from the physician, social worker and nurse and one or more interviews are held with the patient. The patient's social, economic and family background is analyzed, educational and vocational history evaluated and rehabilitation interests and needs are discussed. A personality appraisal is also required. Intelligence, interest and aptitude tests are performed and, in our experience, in 50 per cent of the patients the testing procedures have been indicated and helpful. With this case preparation, constructive, practical rehabilitation and vocational guidance are possible.

The rehabilitation department should have sufficient personnel and adequate physical facilities to test the patients' aptitudes, maintain suitable abilities or teach new skills. We use an occupational therapy department where all the usual arts and crafts are taught. In addition, there are printing, bookbinding, mimeographing and photographic divisions. We also have teachers for academic subjects and stenography and typing. Correspondence courses and necessary text books are employed for special instruction. Patients have been helpful as instructors in English and citizenship. We have also had very satisfactory results with utilization of our regular Sanatorium departments. These facilities are always available for practical training and experience and include the nursing

division, laboratory, clerical and stenographic offices, telephone switchboard, dietary division and other institutional departments.

The rehabilitation needs of the tuberculous have rightly been emphasized. When our patients are assigned to the program, their vocational requirements are routinely determined. Of 945 rehabilitation discharges, 48 per cent required special vocational training to prepare them for suitable or skilled positions. It would have been hazardous for this entire group to return to their former occupations. Twenty-six per cent needed placement but no vocational training, and included mainly those with suitable occupations but no jobs, and those not trainable because of lack of aptitudes, experience, etc. Neither placement nor vocational training was necessary for 26 per cent. This group included patients with suitable jobs and housewives and students.

Every Sanatorium rehabilitation assignment must be for a definite purpose and must fill a specific individual need. It cannot be stressed too strongly how important it is to guide the entire rehabilitation process on this principle—the requirements and objectives of each patient.

The 945 rehabilitation discharges of the past three years were placed in the program for the following reasons: 32 per cent to observe or determine skills; 29 per cent, diversional; 21 per cent, for preliminary training or preparation for employment, and 18 per cent to maintain skills. It is not possible or necessary for the Sanatorium to provide every patient with a completed skill in a particular type of work. If only interests and aptitudes are determined and a decision reached as to what the patients can or cannot do, an important service is accomplished. After such a trial or observation period, required vocational training can be initiated in the Sanatorium or the patient can be properly referred to a rehabilitation training centre after discharge. Moreover, the outside work need not be the same as in the Sanatorium, for if the patient only develops a particular ability, such as manual dexterity, he can readily adapt himself to suitable training or work in line with the developed skill. Assignments made on a diversional basis are also of much value, not only for the physical benefits of rehabilitation, but because they build morale, provide opportunities for study, develop satisfactory hobbies, and for women especially, are useful for household management or responsibilities. This, then, is diversion that is purposeful.

Of the 20 different rehabilitation activities utilized in our program, there are 6 principal ones which include over four-fifths of all the assignments—the occupational therapy shop with 42 per cent and, in decreasing frequency, the nursing division, classes for typing, stenography, academic subjects and English and the Sanatorium offices.

The family should be prepared in advance for the patient's departure from the Sanatorium. We notify the referring or active working agency a month before the expected discharge. The home situation can then be investigated, for there may be social, economic or family problems to be cared for. Without this, it might be very difficult for the patient to become adjusted.

A representative of the State Rehabilitation Bureau routinely visits the Sanatorium to interview the patients to be referred to the Bureau upon discharge.

Delays in post-sanatorium service are thereby avoided and appropriate and effective rehabilitation measures readily devised.

POST-SANATORIUM PHASE

The follow-up period is not less important than the institutional phase of the program and there must be a concrete and directed post-sanatorium plan. At the time of discharge all patients are referred for medical care, and when indicated, to a rehabilitation agency and social service or welfare organization. For rehabilitation assistance we have utilized the State Rehabilitation Bureau, the Tuberculosis and Health Associations of the 5 boroughs of New York City and 6 voluntary agencies.

On discharge, the medical agencies receive the patient's complete medical summary, including rehabilitation progress and representative X-ray films of the hospitalization period. (A similar abstract goes to the rehabilitation organization.) This information helps the outside physician to regulate the patient's work tolerance. The initiation of rehabilitation training and all changes in daily work tolerance must be approved by the physician providing post-sanatorium care. The rehabilitation agencies assign the patients to work shops or rehabilitation centres for vocational or educational training. Part-time, and then full-time placements in industry are arranged. This community rehabilitation service is continued until the individual completes his training, reaches an eight-hour work tolerance, obtains a job and becomes fully adjusted to employment.

Medical, social service and rehabilitation follow-up must be immediate, continuous and complete. Otherwise the post-sanatorium plans will fail. Promptly after discharge we write the working agencies in the City to check the patients' visits. Our rehabilitation counselor holds a follow-up clinic in New York every two weeks. This affords the opportunity to interview discharged patients, contact community agencies, settle specific problems and insures prompt and efficient service.

Rehabilitation is an essential part of the treatment of the tuberculous and it is just as vital to know the status of rehabilitated patients after an adequate observation period as it is to evaluate any other therapeutic group. To appraise properly the rehabilitation services to our patients, follow-up questionnaires are sent each year (and continued for a five-year period) to the physician, rehabilitation agency and the patient.

Our statistics are incomplete as we only have a one year follow-up of 367 rehabilitation discharges and these are presented merely as preliminary figures. The lack of a reply varied from 7 to 24 per cent for the different questions, but the following percentages are based on the entire group: (*1*) 70 per cent had no illness or complications; (*2*) tuberculous conditions occurred in 11 per cent with one death; (*3*) positive sputa were reported in 4 per cent; (*4*) about 75 per cent never had any reduction of work tolerance; 18 patients had been hospitalized; (*5*) just under half were employed on a full-time basis in industry; if housewives and students are included, 58 per cent were on an eight-hour daily work tolerance; (*6*) of those working, four-fifths had occupations which were safe as far as their

tuberculosis was concerned and three-quarters had jobs suitable according to aptitudes or in line with Sanatorium rehabilitation plans. About one-third returned to a more suitable type of work. The occupations covered a varied and wide range.

CONCLUSION

Successful rehabilitation requires a comprehensive and effective sanatorium program and close coöperation between the sanatorium and the community. All of the community services must be integrated to serve the patient and family during all the phases of treatment, from the time of diagnosis until the individual is fully adjusted. Under these conditions patients will accept sanatorium care, remain till their tuberculosis is arrested and follow through with necessary rehabilitation plans.

The rehabilitation program we have outlined attempts, in a practical and efficient manner, "to restore the tuberculous to the fullest physical, mental, social, economic and vocational usefulness of which they are capable."

CONCLUSIONES

El éxito de la rehabilitación depende de un plan sanatorial comprensivo y eficaz y de la íntima cooperación entre el sanatorio y la colectividad. Hay que integrar todos los servicios cívicos para atender al enfermo y a la familia durante todas las fases del tratamiento, desde el momento del diagnóstico hasta que por fin se ajusta el individuo debidamente. En esas condiciones los enfermos aceptarán la asistencia en el sanatorio, permanecerán allí hasta que su tuberculosis se estacione y observarán las medidas necesarias para la rehabilitación.

El plan de rehabilitación bosquejado se propone, en forma práctica y eficaz: "devolver a los tuberculosos la máxima utilidad física, psíquica, social, económica y profesional de que son capaces."

OCCUPATIONAL THERAPY AND REHABILITATION[1]

A. N. AITKEN[2]

Basically a rehabilitation program in a sanatorium is a plan of treatment to counteract the psychosomatic effects of the disease, tuberculosis. It is unfortunate that the term "psychosomatic medicine" had not come into use before the catch-all word "rehabilitation" had become so widely adopted in medical and nonmedical fields. Or rather, if some word had been devised, specifically delineating the treatment of the psychosomatic effects of disease, much confusion and misunderstanding would have been avoided. This is particularly true in the treatment of tuberculosis.

Tuberculosis may produce a wide range of physical handicaps and the patients are subjected to a multitude of emotional disturbances, brought on by a complexity of causative factors, often due to popular misconceptions, false implications and prejudices, handed down through the generations. Many methods have been devised to correct or ameliorate these physical and mental handicaps.

These emotional disturbances begin with the diagnosis of the disease. It is consumption, a thing to be shunned, incurable or leading to a life of uselessness. They are augmented by hospitalization, separation from family and friends, the stigmata of welfare-aid so often needed and all those that go with being a sanatorium inmate. They are exaggerated by our treatment, the necessary emphasis on the communicable nature of the disease and the invalidism which we deliberately develop. Patients become self-conscious, isolated and sensitive, but dependent. They are neurotic, self-centered, selfish, fearful of others, fearful of themselves, fearful of effort. It becomes impressed in them that to keep on living is the only important thing in life. These are disabilities which can be counteracted only by well-timed measures, often devious and unobtrusive, and by constant effort.

In no illness has mass treatment and routine care been more highly developed. In none are patients more regimented, bound by rules of conduct, restricted in activities and associations, subjected to so abnormal a life. In no illness is treatment of the individual more necessary, in which it is more essential to build up an atmosphere of normality. It is prerequisite that patients be adapted to a normal mode of living before they can be safely discharged to their own devices.

The population of a sanatorium is a cross section of the community which it serves. It is composed of ordinary, average people with the same codes of ethics and morals which they had before they became inmates, but with many worries over present and future situations. To bring them back to normal, worries have to be minimized, distorted viewpoints corrected, lost abilities redeveloped or latent abilities utilized. Confidence has to be restored.

[1] Presented before the Medical Section, as part of a symposium on *Medical Management of the Recovery Phases of Tuberculosis*, at the 42nd annual meeting of the National Tuberculosis Association, Buffalo, New York, June 12, 1946.

[2] Sanatorium Director, Niagara Sanatorium, Lockport, New York.

These patients, before discharge, have to be physically reconditioned, mentally and socially readjusted. Some, to become economically independent, need to be vocationally rehabilitated. Though this should be a function of State and Federal Agencies following discharge of the patient, much can be done in pre-vocational and vocational training during the prolonged period of convalescence—with benefit to the morale of the patients and to their mental and social rehabilitation.

For such a program to be fully effective, the combined efforts, not only of the specialists in this work, but also of all hospital employees, are necessary. The attitudes of those giving medical and nursing care, of those in dietary, housekeeping and administration, are as important as those of the rehabilitation workers, the occupational therapists, physiotherapists, social workers, guidance counselors or instructors. The need is to create a normal atmosphere, one approximating life outside. Patients themselves can do much toward creating this atmosphere.

The patients of Niagara Sanatorium, in 1932, formed an association to help in their own rehabilitation and to contrive a form of patient government, this in itself an aid in developing initiative and a sense of responsibility. As it was worded in their constitution, the program was "to help people with tuberculosis to return to a life of healthy, happy usefulness." In this they summed up the full purpose of a medical rehabilitation program.

At first, their efforts were directed mainly towards social activities and training for jobs. It was during the depression; most patients after discharge would have to work. But they were physically fit only for selective work. To obtain this, a skill was necessary and they had had no special training to qualify them for a selective job. This training had to be given before discharge. Sanatorium graduates were not considered by the authorities to be susceptible for vocational rehabilitation nor was their employment considered to be feasible.

Staff members and patients who had something to teach formed classes. All facilities of the Sanatorium were used for physical conditioning and teaching purposes. Instructors were added later from a local adult education program. Some progress was made, principally in building up an interest. A few patients were able to acquire sufficient training to secure jobs, mainly within the Sanatorium. But the work was desultory and without organization.

When an attempt was made to organize a vocational training program, it was found that the number of patients who would receive direct benefit was limited, not over 15 per cent of the total. Some of those left out were interested, even enthusiastic, but under the rules they were not qualified. They were too old or too handicapped, physically or educationally. . Whereas, many, particularly in the younger age group to whom such a program was most applicable, were not interested in being rehabilitated. They wanted something more immediately profitable. Some form of indoctrination and guidance was necessary, as well as a program which would include all groups. Also it had to be made economically attractive to lure them away from the pin money of arts and crafts.

We had an Occupational Therapy Department whose work was limited to arts and crafts. But, as occupational therapy is defined as being "any activity, mental or physical, prescribed and guided to aid in recovery from disease or injury," much of the work being done could be included as therapy. In the case of the old lady with arthritis who took up typing in bed, it was not vocational training but it was occupational therapy. With the girl who was developing her work tolerance as a laboratory assistant and eventually became a medical technologist or the one who went to the record-room and became a medical records librarian, it was not only work therapy, it was also occupational therapy as well as vocational and economic rehabilitation.

So that all patients might benefit from the program, and guidance be started early, it was decided to tie in all patient activities with occupational therapy. Educational, pre-vocational and vocational training and work tolerance projects as well as diversional and social activities were placed under one direction. Vocational instructors and a vocational guidance counselor were added, and it was called the Department of Occupational Therapy and Rehabilitation.

Under this arrangement, instead of waiting until the patient is sufficiently healed to warrant physical effort, counseling and guidance are begun as soon as the patient's physican permits. Not only are diversional activities used, but also aptitude and other psychometric tests frequently are given early, even though vocational training may not be considered, to create interest and build up a new viewpoint. The housewife, beginning with bed-side crafts, can be led into home crafts; sewing classes, housekeeping, foods and cookery, subjects which will simplify her work and make living easier. The high school pupil, interested only in *True Romances* or *Popular Mechanics*, can be induced to continue Spanish or mathematics and complete requirements for graduation.

All patients, irrespective of age, background or extent of disease, are candidates for at least diversional therapy. They are placed by their physicians in a group classification, according to activities permitted. Instruction in hygiene, ethics, hospital routine and the development of a friendly atmosphere is followed by simple diversional activities. When the classification warrants, all patients are interviewed and counseled, various questionnaires completed and the cases discussed in conference as to their medical, social and educational potentialities and their desires. A program is outlined ranging from diversional and social activities to full-time work. Classifications are revised monthly and cases reviewed periodically in conference. To compensate for income lost from neglected craft work, and to avoid the implication of exploitation, patients on work tolerance are paid an hourly wage dependent on the type of work done.

This program lends itself to bed-side instruction as well as to that in classrooms and workshop. It gives an opportunity for patients to be guided individually and for organized group activities. It can range from playing musical selections on the gramophone or book discussions for the bed patient, to field trips, pageants, croquet matches or afternoon tea-parties for those on full exercise. Not only can the patient with chronic fibroid tuberculosis, a perma-

nent patient, be kept occupied but also patients with highly skilled training, the graduate nurse, the doctor, the school teacher, can be benefited. Graduate nurses are a good example. They acquire the patients' viewpoint, get a new slant on public health problems, learn much of the needs in convalescence. Many say their experience has been a beneficial education. Much that cannot be disclosed by tests alone can be learned of patient capacity and capabilities by observation. Patients can be followed from admission through a graduated program to discharge and follow-up, under one control.

Public sanatoria were established and are maintained at public expense for the protection of the community. This is their first duty. Results of their treatment can be measured, to some extent, by the reduction of hazard to the community, through isolation of active cases and prevention of reactivation.

In the time allotted, it is possible to give our results only briefly. During the years 1938 to 1943 the average length of stay of patients receiving collapse therapy, which is 65 per cent of those with tuberculosis, was two years and five months. The readmission rate was 14 per cent, the rate of those leaving against advice was 7 per cent. The relatively low readmission rate is due probably more to length of stay and medical treatment than to the educational program. But the willingness to remain for the prolonged length of stay is due mainly to the overall rehabilitation program and the contentment of the patients with their treatment.

When Doctor Trudeau elaborated the rationale of sanatorium treatment, the principles of this were rest for the disease and education for the patient. To attain full rest, comfort and contentment is indispensible. The patient has to be satisfied that he is being given every opportunity to get better. In a small hospital, as in a small school, it is impractical to have full-time specialists in all lines of work. Many jobs have to be combined. What the combination is, or what it is called, is immaterial. The success of the program depends upon the patients recognizing that they are being treated as rational adults and not automatons, that they are being given the means of again becoming normal, useful citizens. Sanatorium treatment still is rest for the disease and education for the individual.

SUMMARY

Basically a rehabilitation program in a sanatorium is a plan of treatment to counteract the psychosomatic effects of the disease, tuberculosis. In such a program physical retraining, mental and social readjustment are essential and, as an adjuvant to these, vocational training is valuable. To achieve these results, a variety of facilities are available and many methods can be used. As occupational therapy is any activity prescribed and guided for the purpose of contributing to recovery, any of the methods used in such a program can be incorporated in this line of therapy. This type of program, as it is used at Niagara Sanatorium, is described. The results in reducing hazard to the public, by keeping patients satisfied with sanatorium care and by helping prevent post-sanatorium relapse, are presented.

SUMARIO

En el fondo, un plan de rehabilitación en un sanatorio es un sistema terapéutico destinado a contrarrestar los efectos psicosomáticos de la enfermedad: tuberculosis. En un plan de esa naturaleza resultan esenciales el reentrenamiento físico y el reajuste psíquico y social, y como coadyuvante, el adiestramiento profesional es valioso. A fin de obtener ese resultado, hay varios medios disponibles y pueden utilizarse muchos métodos. Dado que la ergoterapia es toda obra prescrita y orientada con el fin de fomentar la reposición, cualquiera de los métodos utilizados en dicho plan, puede constituir parte de la misma. Descríbese aquí un plan de esta clase, tal como se emplea en el Sanatorio Niágara, y preséntanse los resultados obtenidos en lo tocante a disminuir el peligro para el publico, a mantener a los enfermos satisfechos con la asistencia sanatorial y a ayudar a impedir las recidivas postsanatoriales.

STREPTOMYCIN IN MILIARY TUBERCULOSIS

Its Effect on the Pathological Lesions of Generalized Miliary Tuberculosis in Human Beings

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There is convincing evidence that streptomycin exerts a profound regressive and healing action on the morphological aspects of well established tuberculosis in guinea pigs (1, 2). Evidence also has been presented which indicates that a suppressive effect is exerted by this therapeutic agent on a variety of types of human tuberculosis (3). Because of the encouraging results of these studies, any information as to the effect of this drug on the pathological lesions in clinical human tuberculosis would seem to be timely and important.

Estimation of the therapeutic effect of any drug on such a disease as human tuberculosis is extremely difficult. This is especially true in view of the chronicity of most forms of the disease and the known favorable response of the disease to proper diet, collapse therapy and rest in the absence of any treatment with drugs. With these facts in mind, it would seem that more could be learned from testing the drug by administration in comparatively acute and progressive forms of tuberculosis rather than from testing it by administration in tuberculosis characterized by the chronic manifestations. In the past, two of the most fulminating and usually fatal forms of the disease have been miliary tuberculosis and tuberculous meningitis. For this reason, the present study of 5 cases of miliary and meningeal tuberculosis, terminated by death was undertaken with the object of studying the therapeutic effect of streptomycin[2] on the lesions observed in these two forms of the disease.

REPORT OF CASES

Case 1: Clinical aspects: A white female child, nine and a half months old, was examined in June, 1945, because she had come into contact with open pulmonary tuberculosis. It was found that her reaction to tuberculin was positive. A roentgenogram of the thorax made on June 18, 1945, disclosed a primary lesion in the right lung. The child did not exhibit symptoms until two weeks before she entered a hospital; at that time she began to be restless and febrile and to vomit frequently. A second roentgenogram of the thorax made one week before the patient's admission to the hospital showed an increase in the pulmonary infiltration.

The patient was admitted to the hospital on August 2, 1945. She was pale and listless and had a temperature of as high as 102° F. (38.8°C.). Roentgenographic study revealed a large, fairly well circumscribed lesion in the middle field of the right lung. On August 5, generalized twitchings developed, and the child became less responsive. She continued to vomit frequently. Bulging of the anterior fontanelle was noted. Results of labor-

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[2] Supplied by Merck & Co., Inc.; Abbott Laboratories; The Upjohn Company; Eli Lilly and Company; and Parke, Davis & Company.

atory studies of the cerebrospinal fluid were consistent with a diagnosis of tuberculous meningitis. A specimen of the fluid withdrawn on August 7 produced tuberculous lesions after it had been injected into guinea pigs.

Streptomycin was administered intramuscularly from August 5 to August 10. The total daily dose was 1 g., divided into doses administered at intervals of three hours. On August 10, the concentration of streptomycin in the blood serum was 192 micrograms per cubic centimeter. There was no recognizable clinical response to chemotherapy. The child's condition rapidly became worse and she died on August 11, 1945.

Gross pathological aspects: In the base of the upper lobe of the right lung there was a firm, grayish yellow, pyramidal mass 3 by 3 by 4 cm. The apex of the mass extended almost to the hilum of the lung, where there were a number of enlarged, pale, yellowish lymph nodes. The largest of these was 1.5 cm. in diameter. The cut-surface of the mass was firm and pale yellow, and was found to consist of large numbers of smaller conglomerate nodules which appeared to be only partially encapsulated. On the pleural surfaces and also on the cut-surfaces of all lobes of both lungs there were scattered grayish tubercles, none of which was more than 1 mm. in diameter. The cut surfaces of the spleen and liver revealed similar scattered tubercles. One tubercle was observed in the cortex of the left kidney.

There was marked flattening of the convolutions of the brain, with narrowing of the sulci. There was a heavy, fibrinous exudate over the base of the brain; a few small tubercles were observed along the course of the posterior cerebral arteries. The cut-surface of the brain exhibited severe edema and mild dilatation of the ventricles.

Histopathological aspects: In sections of the upper lobe of the right lung there were large, caseous nodules surrounded by poorly developed capsules which consisted of young fibroblasts and giant cells. There were fine deposits of calcium in the centres of these lesions. There were numerous daughter tubercles. These consisted largely of epithelioid cells and giant cells, although a few of the larger ones revealed central caseation. In the hilar lymph nodes draining this portion of the upper lobe of the right lung there was extensive caseation with early central calcification. The caseous portion was surrounded by fibroblasts and giant cells and a thin capsule of collagenous connective tissue. Numerous daughter tubercles were observed. In sections of the middle lobe of the right lung there were numerous epithelioid cell tubercles in which fibroblasts and giant cells likewise were numerous, but caseation or capsule formation was not observed. There were a few peripheral lymphocytes. In sections of the left lung similar tubercles were observed, but there was, in addition, slight encapsulation by collagenous fibers. Nonspecific bronchopneumonia had been present in the lower lobes of both lungs and in the middle lobe of the right lung.

In sections of the spleen and liver there were scattered tubercles consisting of fibroblasts, giant cells and lymphocytes. The cellular elements were intermingled throughout the tubercles. Caseation was not observed except in a single conglomerate tubercle in the spleen. In the spleen most of the tubercles possessed a thin but definite collagenous capsule, but this was absent in the hepatic lesions and poorly developed in the renal tubercles.

Sections of the *pons varolii*, the region of the optic chiasm and the medulla revealed extensive tuberculous meningitis in which fibrinous exudate, caseation necrosis, epithelioid cells, giant cells and fibroblasts were observed. There was extensive involvement of the blood vessels, with necrosis of the walls. There were small tubercles in the *pons varolii* immediately beneath the meningeal exudate and in the floor of the fourth ventricle. Evidence of tuberculous ependymitis was present in the fourth ventricle. Sections

stained by the Ziehl-Neelsen method revealed the presence of tubercle bacilli in the meningeal exudate.

Sections of the seventh and eight cranial nerves on the right side revealed that tuberculous neuritis had been present.

Sections of other organs were not remarkable. At necropsy, specimens of the cerebrospinal fluid and a suspension of material from the pulmonary lesions were inoculated into guinea pigs; they reproduced the disease in these animals.

The following anatomical diagnoses were made: (*1*) primary tuberculosis of the upper lobe of the right lung and hilar lymph nodes; (*2*) miliary tuberculosis of the lungs, liver, spleen and kidneys; (*3*) tuberculous meningitis; and (*4*) bronchopneumonia (bilateral).

Summary of case 1: Miliary tuberculosis developed in a child nine and a half months old who had primary tuberculosis of the upper lobe of the right lung. This child died of tuberculous meningitis. Primary tuberculosis of the lung was known to have been present over a period of three months, but unequivocal symptoms of tuberculous meningitis had been present for only four and a half days prior to death. The child received 4.5 g. of streptomycin during the last four and a half days of her illness. At necropsy there was only slight evidence of healing in the primary lesion and in the hematogenous (miliary) tubercles in the lungs, liver, spleen and kidneys. There was no definite evidence of healing in the meningeal lesions. It is important to note that although treatment with streptomycin was instituted immediately on the appearance of definite symptoms of tuberculous meningitis, there was no recognizable clinical or pathological evidence of therapeutic effect.

Case 2: Clinical aspects: A white female child, fifteen months old, was admitted to a hospital on June 23, 1945, with a diagnosis of generalized miliary tuberculosis and tuberculous meningitis. The baby had been ill for three months. When admitted, the child had a temperature of as high as 104.5° F. (40.3° C.). She was very irritable and had definite nuchal rigidity. Gastric washings secured on June 26, 1945, contained acid-fast bacilli which produced tuberculous lesions when guinea pigs were inoculated with them. Cerebrospinal fluid withdrawn on June 25 produced similar results when guinea pigs were inoculated with it. A culture of *Mycobacterium tuberculosis* recovered from the infected animals was sensitive to 0.78 micrograms of streptomycin per cubic centimeter of medium.

Treatment with streptomycin was begun on June 25. The drug was administered intramuscularly or subcutaneously at intervals of three hours. During the first week, the total daily dose was increased from 1 to 3.2 g. (400 mg. of streptomycin per kilogram of body weight). After the baby had received this high dosage for three days, a toxic erythema developed, for which reason the total daily amount was reduced to 1 g. This daily dose was maintained thereafter. Treatment was suspended from July 18 to July 26. It was discontinued finally on August 19. The total amount of streptomycin administered was 56.6 g., and the total number of days of treatment was forty-eight. Determinations of the concentration of streptomycin in the blood serum varied from 44.7 to 58 micrograms per cubic centimeter. The value for streptomycin in the cerebrospinal fluid ranged from 7.6 to 22 micrograms per cubic centimeter.

Clinical improvement of the patient was noticeable within a week after treatment was begun. The child became alert, responsive and was completely relaxed when the administration of streptomycin was stopped after twenty-four days. During this period

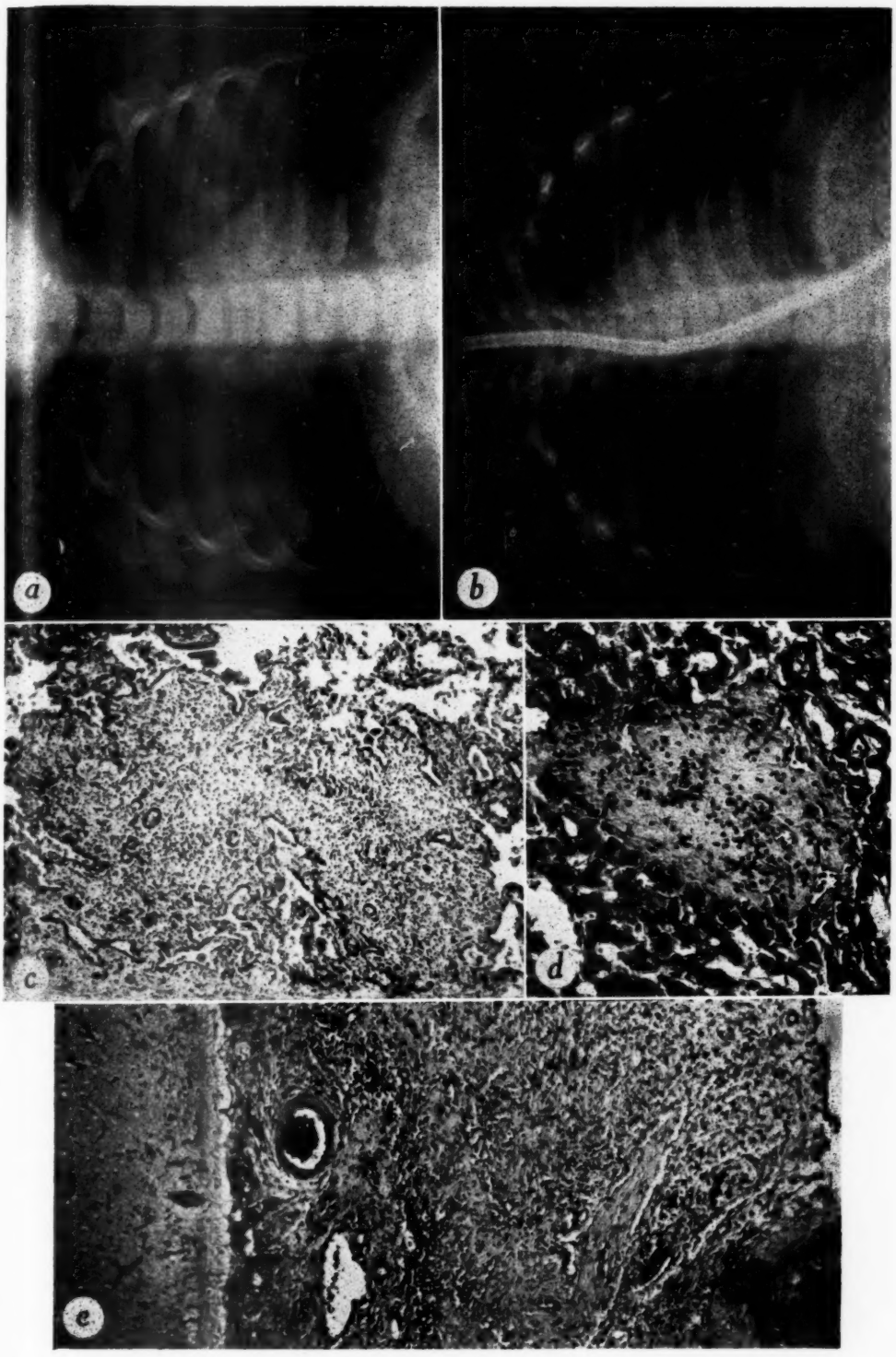

FIG. 1. (Case 2) *a:* Roentgenogram of thorax of patient made on June 23, 1945, before the administration of streptomycin; *b:* roentgenogram of thorax of same patient, made on August 18, 1945, after 56.6 g. of streptomycin had been administered; note marked improvement; *c:* tissue from lung: conglomerate miliary tubercles, with fibrosis and lymphocytes, but no caseation; *d:* tissue from liver: miliary tubercle, revealing fibrosis, hyalinization and lymphocytes; *e:* tissue from brain: tuberculous meningitis; note marked fibroblastic proliferation.

of treatment the cell count of the cerebrospinal fluid, previously as high as 399 cells per cubic millimeter, decreased to 14 cells per cubic millimeter. Specimens of the fluid, when guinea pigs were inoculated with them on July 17 and July 26, did not produce tuberculous lesions. There was marked abatement in the pulmonary tuberculosis, as shown when a roentgenogram made on August 18 is compared with one made when the patient was admitted on June 23 (figures 1*a* and *b*). Moreover, gastric washings injected into guinea pigs on July 26 did not produce tuberculous lesions.

During the week in which chemotherapy was suspended, the symptoms of meningeal irritation, including marked nuchal rigidity, gradually recurred. The cell count of the cerebrospinal fluid became high (as many as 1,700 cells per cubic millimeter), and the value for total protein reached a maximum of 320 mg. per 100 cc. Specimens of cerebrospinal fluid withdrawn on August 20 and August 24 again produced tuberculous lesions when they were injected into guinea pigs. There seemed to be no response to the second course of streptomycin, which included 3 test doses administered intrathecally. Generalized spasticity developed; the child became stuporous and died on August 25, 1945.

Gross pathological aspects: In the superior portion of the lower lobe of the left lung there was a roughly pyramid-shaped region of increased consistency 1.5 by 2.0 by 2.5 cm. Fibrinous exudate over this region was adherent to the parietal pleura. The cut surface of the lung in this region revealed a caseous, yellow, pyramidal mass with the apex of the lesion situated toward the hilum. The lymph nodes at the hilum were greatly enlarged and caseous. The other lobes of the lungs were not remarkable except for the presence of numerous grayish miliary tubercles approximately 1.0 mm. in diameter. Similar miliary tubercles also were observed in the liver and spleen.

Examination of the brain revealed marked flattening of the convolutions and narrowing of the sulci. A heavy, fibrinopurulent exudate was present over the base of the brain. The cut surface of the brain exhibited severe edema and moderate internal hydrocephalus. Examination of the middle and internal ears disclosed that mucopurulent mastoiditis and otitis media had been present on the right side. Suspensions of a hilar lymph node and of the meningeal exudate were injected into guinea pigs and produced tuberculosis in these animals.

Histopathological aspects: Sections of the large caseous mass in the lower lobe of the left lung and in the hilar nodes disclosed slight calcification in the centres of the lesions. At the peripheries were many fibroblasts and a few collagenous fibers interspersed with lymphocytes and a few giant cells. There were many daughter tubercles, some of which revealed caseation, whereas others were fibrotic. No bacilli of tuberculosis could be found in these lesions by the Ziehl-Neelsen method of staining. Miliary (hematogenous) tubercles were found in all lobes of both lungs. These consisted of irregular fibrotic nodules in which lymphocytes were interspersed between the collagenous fibers (figure 1*c*). There was no caseation and only an occasional Langhans giant cell.

In sections of the spleen and liver there were similar irregular fibrotic tubercles (figure 1*d*). There was a mild degree of fatty change in the liver. Sections of other organs were not remarkable except for occasional foci of calcification in the epithelium of some of the collecting tubules of the kidney.

In sections of the brain there was a massive, fibrinopurulent exudate in the meninges at the base; many of the inflammatory cells had been undergoing necrosis. The arteries and veins were involved in the inflammatory process. Extensive organization of the exudate by fibroblastic proliferation was apparent in some sections (fig. 1*c*). Sections stained by the Ziehl-Neelsen technique revealed large numbers of tubercle bacilli. In the right frontal lobe, the midbrain and *pons varolii* there were small regions of necrosis

which were interpreted as infarcts resulting from acute arteritis of the meningeal vessels, although some of them may have been tubercles. In sections of the spinal cord in the lumbar region there were collections of lymphocytes and fibroblasts. In the cervical region were perivascular collections of polymorphonuclear cells and monocytes which were undergoing necrosis.

The following anatomical diagnoses were made: (*1*) primary tuberculosis of the lower lobe of the left lung and hilar lymph nodes with early calcification and encapsulation; (*2*) generalized miliary tuberculosis (lungs, spleen, liver and brain) with evidence of healing in the lungs, spleen and liver; (*3*) tuberculous meningitis with obstruction of the foramina of Luschka and Magendie; (*4*) internal hydrocephalus; and (*5*) mild fatty changes of the liver.

Summary of case 2: Primary tuberculosis, followed by miliary tuberculosis and tuberculous meningitis, developed in a child fifteen months old. The known duration of the illness, to termination, was five months. The child received a total of 56.6 g. of streptomycin over a period of two months. Specimens of cerebrospinal fluid produced tuberculous lesions in guinea pigs on June 25 but did not do so on July 17 and 26. Treatment was interrupted for one week. Specimens of cerebrospinal fluid again produced tuberculous lesions in guinea pigs when the animals were inoculated on August 20 and 24. There was evidence of early calcification in the primary lesions in the lungs and hilar lymph nodes, but there were only poorly developed capsules of collagenous connective tissue at the peripheries of the lesions. There was definite evidence of healing in the miliary (hematogenous) tubercles in the lung, liver, spleen and lymph nodes. These lesions consisted of fibrous connective tissue interspersed with lymphocytes. Section of the brain, however, revealed that extensive organizing tuberculous meningitis had been present with a number of small infarcts, probably the results of inflammatory occlusion of meningeal vessels.

Case 3: Clinical aspects: A white man, 46 years old, admitted on February 12, 1945, was attacked by peritonitis and a retrovesical abscess following cystoscopy on February 15. The patient had undergone nephrectomy on the left in 1937 for renal tuberculosis. Subsequent cystoscopic examinations had revealed tuberculous cystitis. Roentgenograms of the thorax previously had not shown evidence of pulmonary tuberculosis. On March 12, 1945, however, a roentgenogram disclosed early miliary tuberculosis of the lungs. That the process was rapidly becoming more extensive was indicated in roentgenograms made on March 26 and April 9.

Treatment with streptomycin was begun on March 29, 1945. The drug was parenterally administered continuously until June 29, in increasing daily doses of from 1 to 4 g. Just before treatment was discontinued, moderately severe nerve deafness developed. This gradually improved during the following weeks. Streptomycin therapy was resumed on August 18, the patient receiving 1 g. daily intramuscularly until August 31. Vertigo was noted three days after administration of the drug had been reinstituted. It became severe, and results of caloric tests on September 1 disclosed hypo-active labyrinthine function bilaterally. Decrease in acuity of hearing was again noticeable before treatment was stopped.

The total dose of streptomycin administered was 248.9 g., and the total number of days of treatment was 102. Other chemotherapy included a trial of penicillin, administered

from June 5 to June 13, and again from August 11 to August 18. Sulfadiazine, in doses of 30 grains daily, was administered from August 17 to August 30. Pus was aspirated from a periurethral abscess on August 27, and a solution containing 0.2 g. of streptomycin and 200,000 units of penicillin was injected into the cavity of the abscess.

The patient's temperature was elevated throughout his course. Results of examination of the urine were consistently positive for acid-fast bacilli. However, there was no evidence of increased renal damage during treatment with streptomycin. The urinary output was always adequate and the values for blood urea remained within normal limits. There was marked abatement in the patient's miliary tuberculosis, as shown by roentgenograms of the thorax (figures 2*a* and *b*). There was, however, less definite clinical improvement. The patient steadily lost weight and strength, and the signs of peritonitis increased. This presumably was the primary cause of his death on September 9, 1945.

Gross pathological aspects: Approximately 500 cc. of yellow, turbid fluid, containing masses of fibrin was present in the peritoneal cavity. The omentum and the serosa of the small intestine were covered with large numbers of miliary, yellowish white nodules. The loops of small intestine were stuck together by a fibrinopurulent exudate. The pericardial sac contained approximately 150 cc. of clear, straw-colored fluid. The leaflets of the mitral valve of the heart were slightly thickened, and the *chorda tendineae* were slightly shortened and thickened. On the posterior leaflet of the mitral valve there was a thrombotic vegetation, 1.0 by 0.8 cm.

The pleural surfaces of both lungs were adherent to the wall of the chest at the apices. There was a group of three caseocalcareous nodules in the upper lobe of the right lung near the apex; a similar nodule was situated in a hilar lymph node near the bronchus of the upper lobe of this lung. The pleural surfaces of both lungs contained myriads of tiny gray tubercles varying from 1 to 5 mm. in diameter. The cut-surfaces of both lungs revealed large numbers of similar tubercles. The liver and spleen also contained numerous tubercles from 1 to 3 mm. in diameter.

The right kidney weighed 207 g. There were numerous, irregular, sharply outlined, yellowish white areas on the surface, from 2 to 7 mm. in diameter. The cut-surface of the kidney revealed two medullary fibromata and numerous tiny tubercles scattered throughout the cortex and medulla. The pelvis and calices were moderately dilated. The right ureter was obstructed at its site of entrance into the bladder and was moderately dilated above this point.

The bladder contained 20 cc. of cloudy yellow fluid. The mucosa was the site of numerous irregular ulcers up to 5 cm. in diameter. The larger ulcers had eroded deeply into the muscular layer. The bases were covered with shaggy, grayish yellow exudate and necrotic tissue. In the right posterolateral wall was an opening 5 cm. in diameter which communicated with an abscess that was 12 cm. in diameter. The latter contained approximately 200 cc. of cloudy yellow fluid.

The prostate gland was normal in size, but the cut-surface revealed a number of irregular, grayish yellow areas up to 5 mm. in size.

The brain and spinal cord grossly appeared to be normal, except for a small number of grayish white tubercles, 1 to 3 mm. in diameter, situated in the parieto-occipital regions. On the cut surface, these lesions were found to extend deep into the sulci.

Histopathological aspects: In the apex of the upper lobe of the right lung the lesions were large, partially calcified and ossified, and were surrounded by a thick capsule of collagenous connective tissue. The hilar lymph nodes contained some large, old fibrotic hyalinized lesions as well as some more recent miliary tubercles consisting of epithelioid cells and giant cells without central caseation. Sections of both lungs revealed numerous

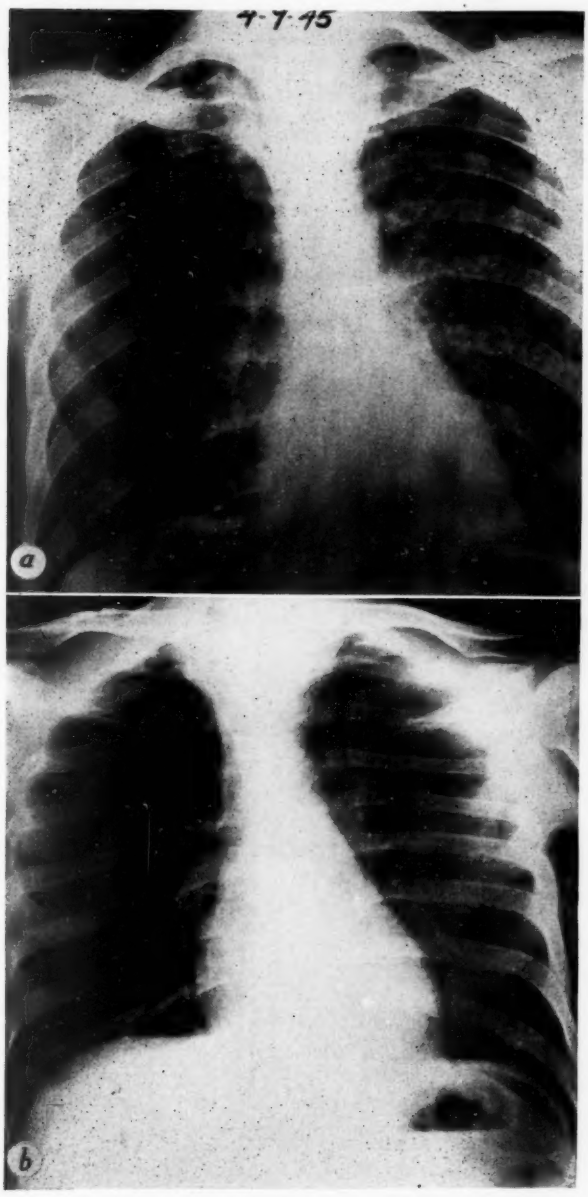

FIG. 2. (Case 3) *a:* Roentgenogram of thorax of patient made on April 9, 1945, before treatment with streptomycin was instituted; *b:* roentgenogram made on August 17, 1945, after treatment with streptomycin had been started.

miliary tubercles, many of which had fused to form conglomerate tubercles. In the right lung, these lesions were characterized by central caseation and thin, poorly developed capsules of connective tissue. There were few epithelioid cells or giant cells. In the left

lung, the lesions also exhibited central caseation, but the connective tissue capsules were much thicker and better developed (figure 3*a*). No tubercle bacilli could be found in any of these lesions by the Ziehl-Neelsen technique.

In the liver, most of the tubercles consisted of epithelioid cells and giant cells. In a few of these, the epithelioid cells in the centres of the lesions had been undergoing necrosis. Many of the tubercles consisted only of connective tissue with interspersed lymphocytes (figure 3*b*).

In the spleen, most of the lesions were conglomerate tubercles consisting of epithelioid and giant cells. Some of these had been undergoing early necrosis (caseation) centrally. None of them had the fibrotic (healed) appearance of those observed in the liver.

In sections of the right kidney, the tubercles revealed central caseation with a peripheral arrangement of epithelioid and giant cells. There was no evidence of formation of a capsule. One small epithelioid cell tubercle was observed in the wall of a vein. In addition to miliary tuberculosis, suppurative pyelonephritis also was present.

Sections of the bladder disclosed extensive tuberculous cystitis that had involved even the muscularis, with much caseation and ulceration. Isolated miliary tubercles consisting of epithelioid cells and giant cells without caseation also were observed. In the submucosa, there was evidence of chronic nonspecific cystitis, characterized by collections of plasma cells, lymphocytes, monocytes, fibroblasts and an occasional polymorphonuclear leukocyte.

The right ureter was the site of an extensive tuberculous lesion which involved the entire wall of the structure. The conglomerate tubercles consisted largely of epithelioid and giant cells and lymphocytes.

Sections of the prostate gland revealed a large area of caseation surrounded by fibrous connective tissue. There was slight calcification at the periphery of the caseous area. Other isolated miliary tubercles contained early necrosis, epithelioid and giant cells, whereas some conglomerate tubercles were completely fibrotic.

One isolated caseous tubercle without a capsule was found in the right adrenal gland. Sections of the ileum and omentum revealed miliary tubercles made up of epithelioid and giant cells, as well as a suppurative inflammatory process.

Sections of the mitral valve exhibited fibrosis and vascularization of the leaflet and an organizing platelet thrombus.

In sections of the brain the only evidence of tuberculous meningitis occurred deep in the sulci of the right parietal lobe (figure 3*c*). Considerable caseation was associated with a fibrinopurulent exudate. The blood vessels and the adjacent cortex were involved by direct extension of this inflammatory process. Many of the vessels were occluded by organizing thrombi. Typical tubercles composed of epithelioid cells also were observed. One of these was present in the left internal capsule. Sections from the surface of the brains, *pons varolii*, medulla and spinal cord revealed only a few perivascular lymphocytes in the meninges.

The following anatomical diagnoses were made: (*1*) previous (eight years) nephrectomy on the left for tuberculosis of left kidney; (*2*) chronic tuberculosis of bladder with ulceration and perforation; (*3*) perivesical abscess with general peritonitis (tuberculous and suppurative); (*4*) generalized miliary tuberculosis with evidence of healing of some lesions in lungs and liver; (*5*) chronic tuberculous meningitis; (*6*) tuberculosis of the right ureter with obstruction; (*7*) hydronephrosis and suppurative pyelonephritis of the right kidney; (*8*) healed rheumatic mitral endocarditis with organized thrombus; and (*9*) emaciation.

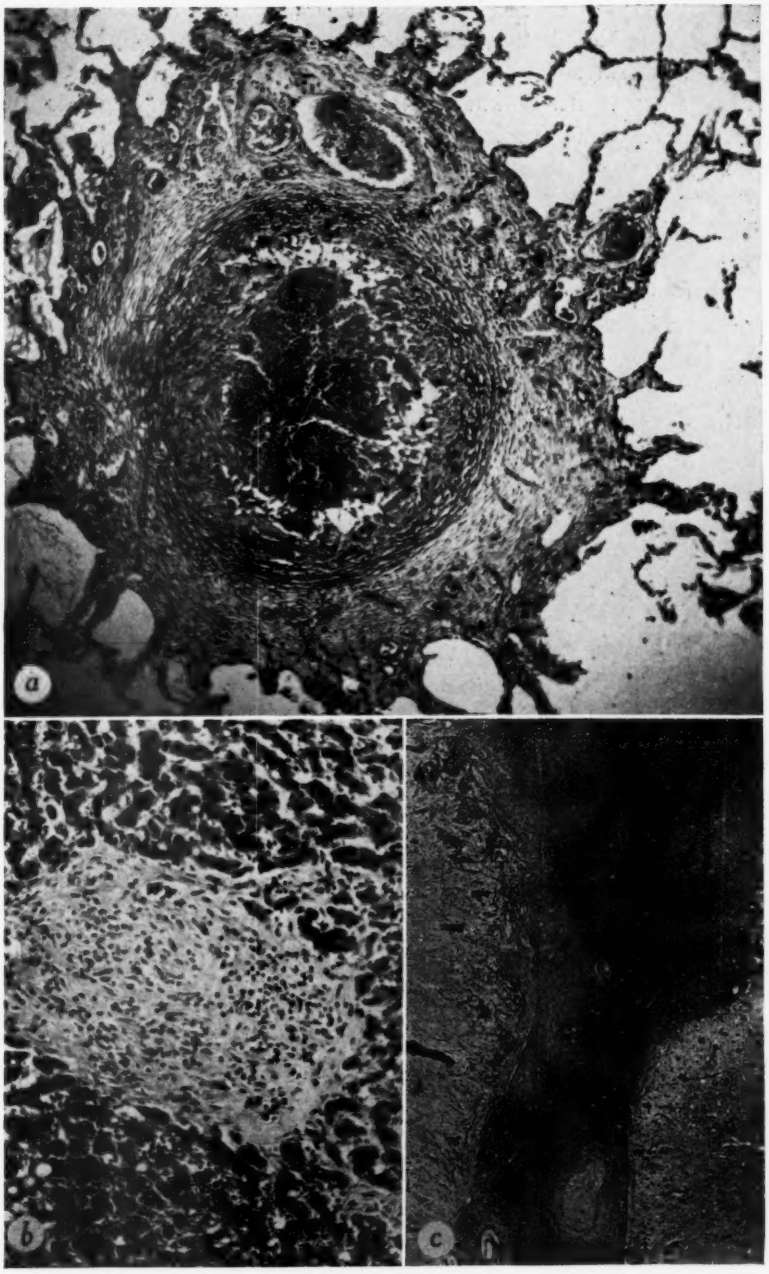

FIG. 3. (Case 3) *a:* Miliary tubercle in lung. There is central caseation but healing is indicated by the wide zone of fibrous connective tissue surrounding the caseous portion; *b:* miliary tubercle in liver undergoing fibrosis; *c:* tuberculous meningitis in a sulcus of the right parietal lobe, with extension to brain.

Summary of case 3: A man, 46 years old, had undergone nephrectomy for tuberculosis of the left kidney eight years before he was admitted to the Mayo Clinic with tuberculosis of the urinary bladder. He died after perforation of a tuberculous ulcer of the bladder, with the development of general tuberculous and suppurative peritonitis and generalized miliary tuberculosis. He received approximately 248.9 g. of streptomycin over a period of 102 days. Some of the tubercles in the lungs and liver exhibited definite evidence of healing with fibrosis and encapsulation. Other tubercles in these same organs, however, and especially in the spleen, kidney, bladder and prostate gland, revealed caseation and histological evidence of progression. Sections of the meninges over the brain and spinal cord revealed mild chronic meningitis without tubercles on the surface. Histologically, there was insufficient evidence to permit the making of a diagnosis of tuberculous meningitis. Deep in the sulci of the cerebrum, however, active caseating tuberculous lesions involving the meninges and adjacent portion of the brain were found.

Case 4: Clinical aspects: A white man, 32 years old, was admitted to a hospital on September 20, 1945, with a diagnosis of miliary tuberculosis. His illness dated from March, 1945, when he had had a "chest cold" that had been followed in April by pleural effusion. In August the patient had become acutely ill, with chills, temperature of as much as 106° F. (41.1° C.), increasing weakness, cough and rapid loss of weight. He had entered a sanatorium, where roentgenograms of the thorax, made on August 18, had disclosed extensive miliary tuberculosis that had not been present in previous roentgenograms. Culture of specimens of the residual pleural fluid produced *Mycobacterium tuberculosis*.

The patient was referred to the Mayo Clinic for treatment with streptomycin. Most of the time the drug was administered intramuscularly at intervals of three hours; occasionally, the continuous intravenous drip method was substituted. The patient received an average daily dose of over 4 g. for a total of forty-one days (from September 23, to November 2, 1945). The concentration of streptomycin in the blood serum varied from 5.0 to 147 micrograms per cubic centimeter of blood; the highest concentration of streptomycin in the cerebrospinal fluid was 59.7 micrograms per cubic centimeter.

Four days after he had been admitted, the patient became mentally confused, and began to complain of stiffness of the neck and headache. A diagnosis of tuberculous meningo-encephalitis was made. On October 16, specimens of cerebrospinal fluid produced the lesions of tuberculosis when injected into guinea pigs. During treatment of the patient with streptomycin the protein content of the cerebrospinal fluid decreased from 240 to 50 mg. per 100 cc., the cell count decreased from 89 to 9 cells per cubic millimeter, and a specimen of cerebrospinal fluid withdrawn on October 30 did not produce tuberculous lesions in guinea pigs. Foci of choroiditis noted on September 21, and at that time thought to be miliary tuberculosis, showed a definite trend toward healing in subsequent funduscopic examination. During the five weeks of treatment there was remarkable clearing of the miliary pulmonary infiltrations as shown by serial roentgenograms (figures 4*a* and *b*). The patient's temperature, previously as high as 102.6° F. (39.2° C.), steadily decreased and did not increase to more than 98.6° F. (37° C.) between October 11 and October 22. Clinically, however, the patient's condition never was promising. He continued to be disoriented, delirious at times, and had some difficulty with articulation and swallowing. Nerve deafness to low tones developed after ten days of chemotherapy.

Before treatment, results of urinalysis had been essentially negative, although at the time the patient was admitted a specimen of urinary sediment produced tuberculosis when injected into guinea pigs. During treatment, albuminuria of grade 2 to 3, cylin-

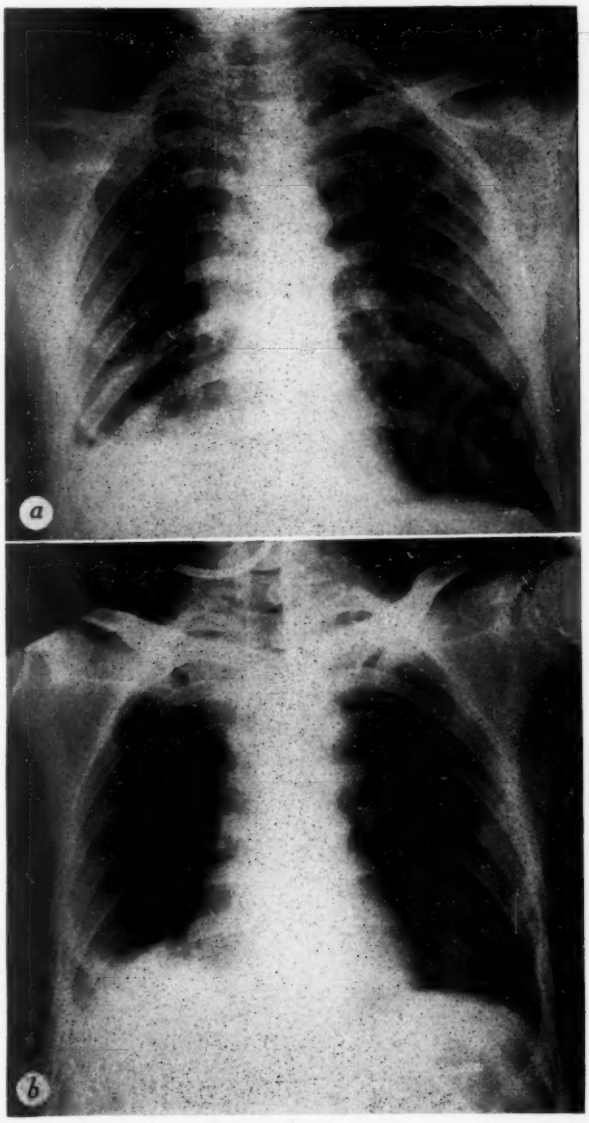

FIG. 4. (Case 4) *a:* Roentgenogram of thorax of patient made on September 21, 1945, showing miliary tuberculosis of the lungs; *b:* roentgenogram made on October 24, 1945, after treatment with streptomycin; note marked improvement.

druria of grade 1 to 3, and hematuria of grade 1 to 4 were noted (grading in each case is on the basis of 1 to 4, in which 1 is least severe and 4 is most severe). Occasionally there was gross hematuria. The blood urea increased from 28 to 90 mg. per 100 cc., al-

though the urinary output remained good. Because it was feared that streptomycin or some impurity in the preparations used was causing renal damage, administration of the

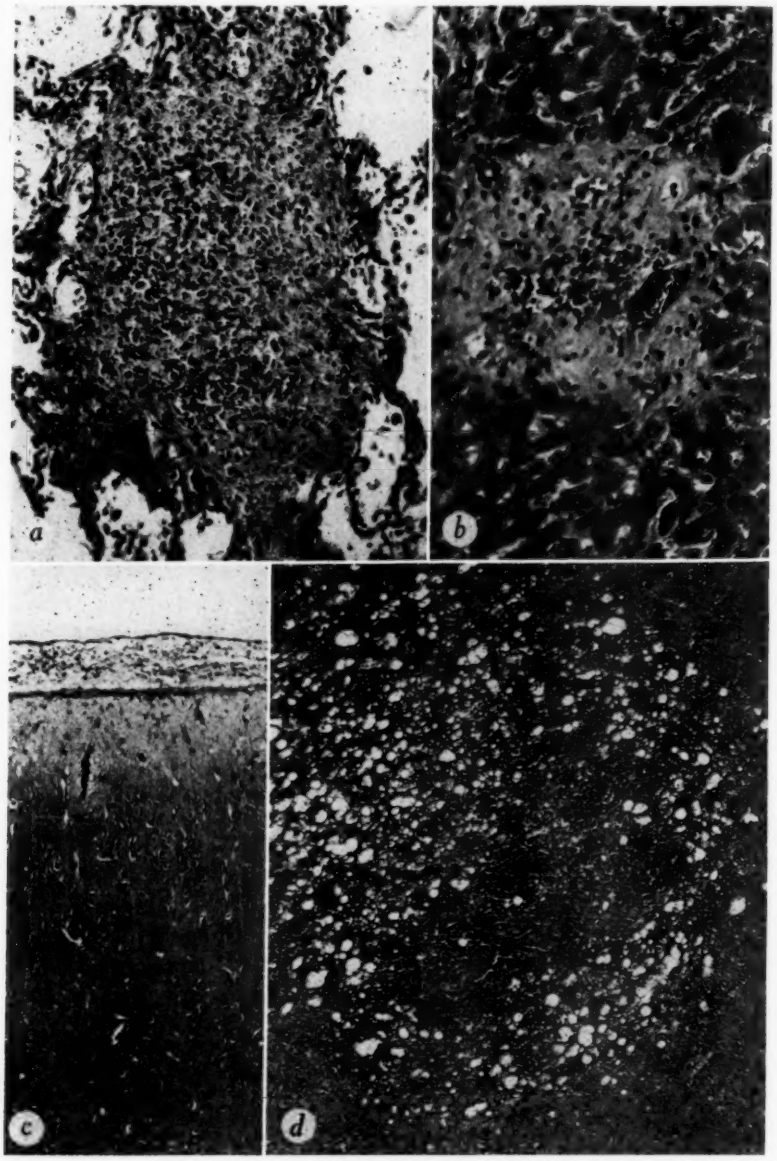

FIG. 5. (Case 4) *a:* Miliary tubercle of lung undergoing fibrosis; *b:* miliary tubercle of liver undergoing fibrosis and hyalinization; *c:* surface of brain: small number of lymphocytes and fibroblasts in meninges; *d:* tuberculous necrosis in brain.

drug was discontinued on October 25. The patient's temperature soon became elevated, and administration of the drug was reinstituted on October 28.

The patient continued to fail and died on November 2, 1945.

Gross pathological aspects: The right pleural cavity was largely obliterated by dense adhesions with loculated fluid. The pleura over the right lung was irregularly thickened to as much as 5 mm., and the cut-surface exhibited yellowish streaks. The left pleural cavity contained 250 cc. of bloody fluid and a few fibrinous adhesions, posterolaterally. The cut-surface of both lungs disclosed numerous tiny grayish tubercles. Similar lesions also were observed in the liver and spleen. There were submucosal hemorrhages in the pelves of both kidneys. The right kidney weighed 200 g. and the left kidney weighed 229 g. In the cerebrum, *pons varolii* and cerebellum there were small, yellowish, irregular regions of necrosis up to 5 mm. in diameter. No evidence of meningitis was observed.

Histopathological aspects: Sections of the lungs disclosed marked thickening of the pleural surfaces by fibrous connective tissue. Superimposed on the collagenous and partially hyalinized connective tissue was a more recent fibrinous exudate. In a section of a hilar lymph node a 2 mm. nodule with a caseous centre and a thick hyalinized connective tissue capsule was found. Numerous poorly delineated miliary tubercles which consisted largely of fibroblasts, collagen fibers and many lymphocytes were present in all lobes of both lungs. An occasional monocyte and epithelioid or giant cell, but no caseation, could be observed. In most of the lesions, no definite capsule had been formed, and the diffuse fibrosis of the entire lesion suggested that the healing process had been too rapid for the development of either caseation or encapsulation (figure 5*a*). Tubercle bacilli could not be found in material from these lesions by the Ziehl-Neelsen technique. In the liver and spleen similar, poorly delineated tubercles, consisting almost entirely of fibrous connective tissue and lymphocytes, were observed (figure 5*b*).

In sections of the kidneys there was severe hyaline granular degeneration of the tubular epithelium with sloughing of the cells. Many tubules were filled with albuminous and granular casts. A considerable number of tubules were lined by newly formed flat epithelial cells. There were focal interstitial collections of fibroblasts and lymphocytes. Focal interstitial calcification occasionally was observed.

In sections of the brain and spinal cord obtained from many locations only scattered lymphocytes and fibroblasts could be found in the meninges (figure 5*c*). In the substance of the brain in the frontal, parietal and occipital lobes, *pons varolii*, cerebellum and medulla were regions of necrosis surrounded by an internal zone of phagocytes filled with lipoid and an external zone of fibroblasts, lymphocytes and numerous capillaries (figure 5*d*). Ziehl-Neelsen stain revealed numerous tubercle bacilli in these lesions.

The following anatomical diagnoses were made: (*1*) chronic tuberculous pleuritis on the right; (*2*) miliary tuberculosis of the lungs, spleen, liver and brain with evidence of healing of lesions in lungs, liver and spleen; and (*3*) acute tubular nephritis.

Summary of case 4: A man, 32 years old, in whom tuberculous pleuritis had developed in March 1945 was found in August of that year to have miliary tuberculosis. He received 177 g. of streptomycin over a period of approximately six weeks. During this course of treatment, his temperature became normal, the cerebrospinal fluid, a specimen of which had caused tuberculosis when it was injected into a guinea pig, became normal and lesions in the choroid and lungs exhibited definite regression. Evidence of renal damage occurred during the course of treatment. Death occurred after a total illness of approximately eight months. Necropsy revealed evidence of healing in the miliary tubercles in the lungs, liver and spleen. There was no evidence of tuberculous meningitis, but active widespread tuberculous lesions were found throughout the brain.

Case 5: Clinical aspects: A white boy, 14 years old, entered a hospital on October 5, 1945. The diagnosis at the time of admission was generalized miliary tuberculosis. The boy's illness had begun three months previously, with such symptoms as fever, cough, anorexia

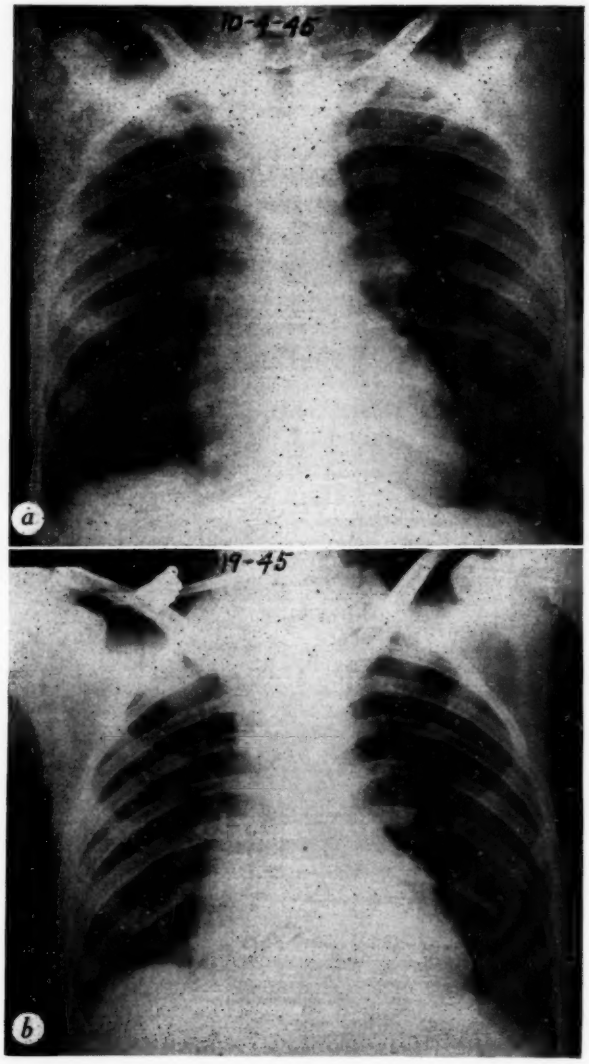

FIG. 6. (Case 5) *a:* Roentgenogram of thorax of patient made on October 4, 1945, showing miliary tuberculosis of the lungs; *b:* roentgenogram made on November 19, 1945; note definite improvement after treatment with streptomycin.

and loss of weight. According to his history, a roentgenogram of the thorax, made on August 1, 1945, had been reported as indicating no abnormality. The next roentgenogram, made on September 15, 1945, had showed miliary pulmonary tuberculosis and a notching of the ribs which was regarded as characteristic of coarctation of the aorta.

When admitted, the patient was acutely ill, with a temperature of 103° F. (39.4° C.). Culture of gastric washings produced *Mycobacterium tuberculosis*. Examination of the ocular fundi disclosed numerous miliary tubercles in various stages of healing in the choroid layer of each eye. The patient was mentally confused and, within a few days after admission, he began to exhibit symptoms of dysphagia and dysarthria. Spinal puncture was done several times, but no definite evidence of meningitis was secured thereby. However, guinea pigs inoculated with specimens of the cerebrospinal fluid on October 13, 1945, subsequently exhibited tuberculous lesions.

Administration of streptomycin was begun on October 5. The drug was administered by intravenous drip or intramuscularly at intervals of three hours. The dose was large, varying from 2 to 10 g. daily. The total dose was 242.5 g. and the total number of days of treatment was forty-two. The content of streptomycin in the blood serum varied from 22.5 to 113.6 micrograms per cubic centimeter. When the concentration of streptomycin in the blood was highest, the concentration in the cerebrospinal fluid was 22 micrograms per cubic centimeter. The only other specific treatment was a course of 4,2′-diamino-phenyl-5′-thiazolyl sulfone (promizole) given orally in doses of 3 to 12 g. daily, from October 13 to 22.

During treatment there was marked abatement of the pulmonary tuberculosis, as shown by roentgenograms of the thorax (figures 6*a* and *b*). Repeated examination of the ocular fundi showed an increased tendency toward healing of the tubercles that had been noted at the first examination. The patient's temperature decreased somewhat, but otherwise there was no clinical improvement. He continued to be disoriented and to have a slurred, nasal type of speech. On the second day of treatment, he complained of tinnitus, and on the tenth day, reduction of hearing acuity was noted. The latter was suspected of being an effect of streptomycin. The administration of streptomycin was discontinued from November 12 to 22 so that it might be determined whether or not the patient's general decline had been caused by the toxicity of the drug. During this time his condition became worse and he died on November 24, 1945, two days after chemotherapy had been resumed.

Gross pathological aspects: The heart weighed 494 g. At the isthmus of the aorta, immediately distal to the occluded opening of the obliterated ductus arteriosus, was a marked narrowing of the aorta. The circumference of the aorta at this point was 1.3 cm., whereas immediately above the aortic valve the circumference was 6.0 cm. Distal to the stenotic portion of the aorta, the aorta was hypoplastic.

Both lungs contained widely scattered, grayish miliary tubercles, most of which were approximately 1 mm. in diameter. Caseous necrotic lesions with poorly defined capsules were seen in the hilar lymph nodes.

Miliary tubercles were present throughout the liver, spleen and kidneys. A number of infarcts, 5 to 12 cm. in diameter, were present in the spleen.

Examination of the brain and spinal cord disclosed no gross evidence of meningitis. On section, however, multiple grayish yellow tubercles up to 2 mm. in diameter were observed in the cerebral hemispheres, *pons varolii* and cerebellum. Some of these tiny lesions were surrounded by a narrow, hemorrhagic zone.

Suspensions of material from the lungs and brain secured at necropsy were injected into guinea pigs and produced tuberculosis in these animals.

Histopathological aspects: Sections of the hilar lymph nodes contained large regions of caseation surrounded by a relatively thin, collagenous connective tissue capsule. Fine deposits of calcium salts were present in the caseous portions. Small hyaline scars which may have represented healed daughter tubercles were present in lymph nodes adjacent to

the capsules of the larger lesions. Most of the miliary tubercles in the lungs consisted of irregular fibrous nodules containing lymphocytes and occasional epithelioid and giant

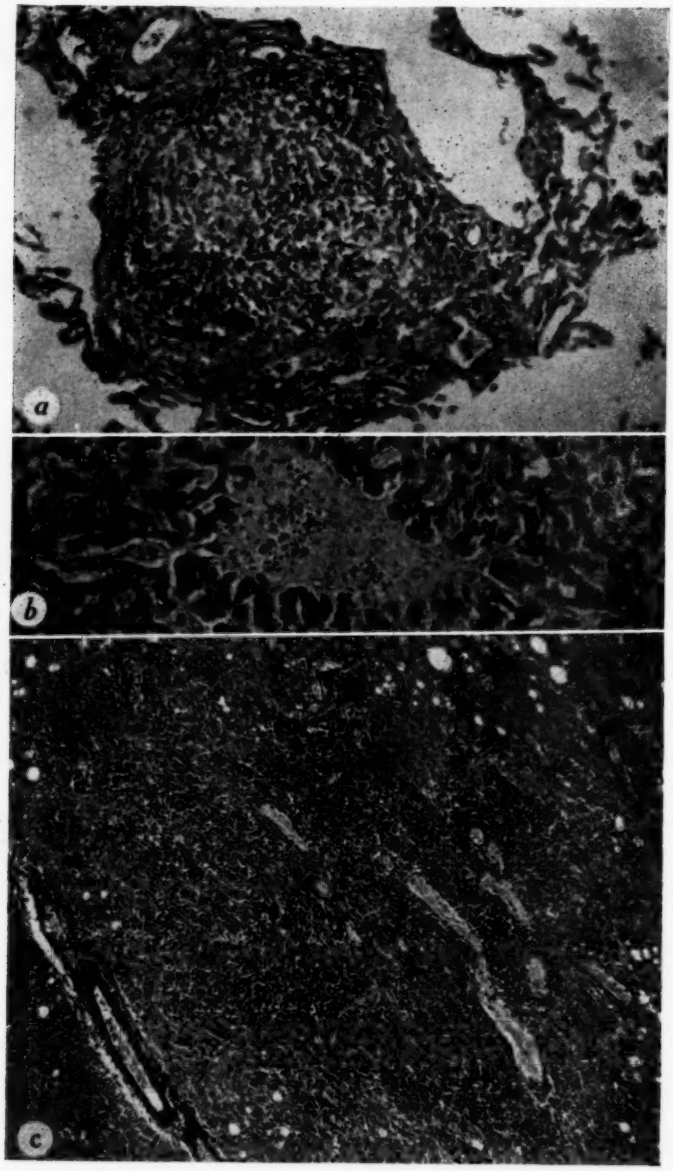

FIG. 7. (Case 5) *a:* Miliary tubercle of lung: note proliferation of fibroblasts and numerous lymphocytes; *b:* miliary tubercle of liver; note fibrosis and hyalinization; *c:* active tuberculous lesion of the brain.

cells (figure 7*a*). None of the lesions revealed any evidence of necrosis or caseation, but tubercle bacilli were demonstrated in some of these lesions by the Ziehl-Neelsen stain.

In the sections of the spleen and liver, the tubercles consisted of irregular nodules of fibrous connective tissue, with a few scattered lymphocytes (figure 7*b*).

In the right kidney, the tubercles consisted largely of fibrous connective tissue with a few epithelioid cells. In the left kidney and the prostate gland, however, many of the tubercles exhibited evidence of caseation without encapsulation, and tubercle bacilli could be demonstrated in material from these lesions by Ziehl-Neelsen stain. In the prostate gland, the regions of caseation were particularly extensive and there appeared to have been little or no inhibition of the progress of the disease in this organ.

Miliary tubercles revealing definite evidence of fibrosis and healing also were present in the thyroid and thymus glands and in the diaphragm.

Numerous sections from the cerebrum, *pons varolii*, cerebellum and spinal cord revealed no evidence of meningitis. In a single section from the right frontal lobe, however, a small collection of epithelioid cells with one giant cell was found. In the substance of the brain in the frontal, parietal and occipital lobes, in the basal nuclei, *pons varolii* and cerebellum, there were numerous lesions consisting largely of epithelioid cells, fibroblasts and giant cells with many lymphocytes and plasma cells, without evidence of necrosis or encapsulation (figure 7*c*). Neighboring blood vessels usually were surrounded by a zone of lymphocytes. Many tubercle bacilli were demonstrated in these lesions by the Ziehl-Neelsen stain.

The following anatomical diagnoses were made: (*1*) chronic primary tuberculosis of the hilar lymph nodes with early calcification and encapsulation; (*2*) generalized miliary tuberculosis of the lungs, liver, spleen, kidneys, prostate gland, eye and brain, with evidence of healing in the lesions of the lungs, liver, spleen and kidneys; (*3*) stenosis of the isthmus of the aorta with hypertrophy of the heart; and (*4*) infarcts in the spleen.

Summary of case 5: In July, 1945, tuberculosis of the hilar and mediastinal lymph nodes developed in a boy, 14 years old. Miliary tuberculosis of the lungs was discovered on September 15. The patient received 242.5 g. of streptomycin over a period of approximately six weeks. Regression of the pulmonary and fundic lesions and a decrease in temperature occurred during this period, without other definite signs of clinical improvement, however. At necropsy there was evidence of regression and healing in the lesions of the hilar nodes, lungs, liver, spleen and right kidney. The lesions in the left kidney, prostate gland and brain, however, were active and progressive. The presence of extensive tuberculous lesions in the brain in the absence of tuberculous meningitis appeared unique.

COMMENT

In our opinion, these cases present encouraging histopathological evidence of an inhibitory action exerted by streptomycin on human miliary tuberculosis and tuberculous meningitis. In all the patients, with the exception of case 1, who received treatment for only a five-day period, there was convincing evidence of regression and healing in the miliary tubercles of the lungs, liver and spleen. By healing, we do not imply destruction of all the tubercle bacilli in the lesions, since these organisms were demonstrated at necropsy either by appropriate stains or by results of inoculation of guinea pigs with appropriate specimens in cases 1, 2 and 5. By healing we do mean the occurrence of fibrosis, hyalinization and the absence of caseation in the miliary tubercles. These regressive changes were particularly pronounced in the lungs, liver and spleen of patients 2, 4 and 5

and in the lungs and liver of patient 3. The regressive changes did not appear to follow the usual pattern of encapsulation of a cellular or caseous central mass, but represented, rather, a diffuse, even fibrosis of the entire lesion. This suggested that healing had occurred so rapidly that the usual sequence of central caseation and peripheral encapsulation did not have an opportunity to develop. The regressive changes in these lesions resulted in the formation of irregular fibrotic scars with rough or angular borders, rather than the typical, more nearly spherical, lesions usually observed in miliary tuberculosis.

Although there have been reports of healed miliary tuberculosis (Rich (4), Fishberg (5), Waller (6), Wunderlich (7), Burkart (8), Pinner (9)), the phenomenon nevertheless is rare. The lesions of the 2 patients observed by Rich (4) were less profuse than those in the usual case of fatal miliary tuberculosis; Rich said that the condition in such cases would be more properly designated as "disseminated tuberculosis," and that he would reserve the term "miliary tuberculosis" to identify the condition in which the tissues are more thickly studded with tubercles. This thick studding with tubercles was a feature in all our cases.

In support of the argument that the miliary tubercles in the organs of our patients were regressing and healing, there is also considerable accessory evidence in the clinical, roentgenological and laboratory data in all cases except the first. In case 2, clinical improvement was apparent within one week after treatment with streptomycin had been started. In this case specimens of cerebrospinal fluid and gastric washings, after a period of treatment, did not produce tuberculous lesions when guinea pigs were inoculated with them. Roentgenograms of the thorax likewise revealed marked improvement. In case 3, roentgenograms of the thorax disclosed definite improvement in the pulmonary miliary lesions. In case 4, there was little clinical improvement, but the temperature decreased to normal, the lesions in the choroid layer of the eye underwent healing and specimens of cerebrospinal fluid, while the patient was undergoing treatment, did not produce tuberculous lesions when guinea pigs were inoculated with them. Serial roentgenograms of the thorax likewise indicated marked abatement of the pulmonary tubercles. In case 5, likewise, the patient presented no evidence of clinical improvement, but his temperature decreased and the lesions in the choroid layer of the eye regressed. The roentgenograms of the thorax in this case also revealed striking evidence of improvement.

Although there was definite evidence of healing in the miliary tubercles of the lungs, liver and spleen in most of our cases, it is important also to note the lack of significant histological signs of regression in the lesions of the primary complex of the lungs and hilar nodes in cases 1, 2 and 5, and also in the hematogenous lesions of the kidney in cases 3 and 5, prostate gland in cases 3 and 5, adrenal glands and bladder in case 3, meninges in cases 1, 2 and 3, and especially in the brain in cases 1, 3, 4, and 5.

The fact that tuberculous lesions may heal in one organ or some organs, whereas active progression occurs in others, is not a new observation. It is a phenomenon which has been well recognized for many years, but has been difficult

to explain. Among the factors which investigators have found to be of importance are such mechanical ones as location of the organ, circulation of blood and lymph and anatomical and histological structure. In addition to these, Rich has indicated that there are inherent differences in the native resistance of different organs. He has pointed out that although the lungs, spleen and liver always contain innumerable tubercles in the presence of miliary tuberculosis, the lung frequently is the site of extensive lesions, whereas the spleen and liver are not. Moreover, such organs as the kidney, adrenal and prostate glands and brain are only slightly involved in miliary tuberculosis, but frequently are the sites of extensive lesions in non-miliary tuberculosis. It is to be noted that the latter organs were the ones in which there was little or no evidence of healing in our cases.

In addition to the mechanical factors and the inherent differences in the native resistance of different organs, two other factors seemed to us to be of

TABLE 1

*The content of streptomycin at necropsy in various tissues and fluids in case 5.**

TISSUE OR FLUID	MICROGRAMS PER G.
Urine	3,507
Blood serum	120
Kidney	172.8
Lung	42
Spleen	20.6
Liver	16.9
Cerebrospinal fluid	15.8
Brain	None

* Dose: 0.833 g. given intramuscularly every two hours for 9 doses (equivalent to 10.0 g. or 10 million S units per day). (This dose given during eighteen hours prior to death.)

importance: (*1*) the size or mass of the lesion at the time that treatment with streptomycin was instituted, and (*2*) the concentration of streptomycin in fluids and tissues.

It is to be noted that the best evidence of healing occurred in the comparatively minute miliary lesions, whether these occurred in the lungs, liver or spleen, whereas the larger lesions, such as those of the primary complex in the lungs and hilar nodes and the large lesions in the bladder and prostate gland, exhibited little or no evidence of regression. It may be that an effective concentration of streptomycin readily penetrates the relatively small miliary lesions, but is unable to reach the larger necrotic masses in which tubercle bacilli continue to multiply.

The concentration of streptomycin, as determined by our colleague Dr. F. R. Heilman, in various tissues and fluids at necropsy in case 5, is shown in table 1. The most striking fact about these results is the presence of a significant concentration of streptomycin in the cerebrospinal fluid in contrast to its complete absence in the brain. Similar observations have been recorded by Adcock (10). This is undoubtedly of great importance in explaining the presence of pro-

gressive, active lesions of the brain in the absence of tuberculous meningitis in cases 4 and 5. It probably also helps to explain the histological evidences of organization of meningeal tuberculosis in case 2 and the absence of meningeal lesions on the surface of the brain in case 3. The relatively high concentration of streptomycin in the urine and in the kidneys emphasizes the point that other factors in addition to the concentration of the drug must be considered in explaining the relative absence of healing in the lesions of the kidneys and bladder.

Although there are cases on record (Macgregor and Green (11), and McMahon (12)) in which tuberculous meningitis has regressed or healed, the phenomenon is certainly rare. For this reason, we believe the character and distribution of the lesions in the central nervous system in cases 3, 4 and 5 are unique. In case 3, there was no evidence of meningitis on the surface of the brain or spinal cord, and the only lesions which could be found occurred deep in the sulci of the right parietal lobe, a location which streptomycin presumably could not reach. In case 4, the cerebrospinal fluid became normal during treatment, and no evidence of meningitis could be found at necropsy, although there were extensive lesions in the brain. In case 5, also, there was no evidence of meningitis at necropsy, but wide-spread lesions were present in the brain. The presence of significant concentrations of streptomycin in the cerebrospinal fluid and the complete absence of streptomycin in the brain undoubtedly explain these unusual findings. The question as to why streptomycin appears in the cerebrospinal fluid but not in the brain remains unanswered. It has been postulated that a so-called pia-glial barrier exists which prevents certain dyes and the serum bilirubin of jaundiced patients from reaching nerve tissue. Perhaps a similar mechanism is responsible for the inability of streptomycin to penetrate the substance of the brain.

Although attention has been centered in this study on the effect of streptomycin on the lesions of tuberculosis, it is extremely important also to point out that, except in case 4, there was no histological evidence of a toxic effect of the drug on any of the organs. In case 4, the degenerative changes in the renal tubular epithelium suggested a toxic effect of the drug or of some impurities associated with the drug. That some impurities in the streptomycin were responsible in this one case appears likely in view of the absence of demonstrable renal damage in the other cases.

From a clinical standpoint, the nerve deafness and the mental confusion and delirium of the patients who received the drug appeared extremely important and demanded an explanation. Actual tuberculous involvement of the eighth (acoustic) nerve was demonstrated only in case 1. In case 3, no lesions could be demonstrated to account for the deafness. In cases 4 and 5, there were extensive lesions in the *pons varolii* which might have been responsible. The mental confusion probably was the result of the meningitis in cases 1 and 2 or the lesions in the brain in cases 4 and 5. In case 3, mental confusion could have been caused either by meningitis or the lesions in the brain. None of these patients received streptomycin intrathecally for any significant period of time.

Subsequent experience with another series of patients with tuberculous meningitis treated by both the parenteral and intrathecal administration of streptomycin has apparently yielded superior results (3).

SUMMARY AND CONCLUSIONS

Clinical, roentgenological and pathological observations concerning 5 patients who had fatal miliary tuberculosis treated with streptomycin are reported. Evidence of regression and healing of the miliary tubercles in the lungs was observed roentgenologically in 4 cases, ophthalmoscopically in the choroid layer of the eye in 2 cases and histologically in the lungs and liver in 4 cases and in the spleen in 3 cases. The development of widespread tuberculous meningitis apparently was inhibited in one case and was either prevented or cured in 2 other cases. No histological evidence of any toxic effect of the drug could be found, with the possible exception of renal tubular damage which occurred in one case. These observations offer further encouraging evidence of the therapeutic efficacy of streptomycin in tuberculosis. They also offer some hope for the effective treatment of two hitherto consistently fatal forms of the disease.

SUMARIO Y CONCLUSIONES

Comunícanse observaciones clínicas, radiológicas y patológicas en 5 enfermos que padecían de granulia letal y fueron tratados con estreptomicina. Observáronse signos de regresión y cicatrización de los tubérculos miliares en los pulmones, radiológicamente, en 4 casos, oftalmoscópicamente, en la capa coroides del ojo en 2 casos, e histológicamente en los pulmones e hígado en 4 casos, y en el bazo, en 3. En un caso aparentemente se inhibió la producción de una meningitis tuberculosa difusa, y en otros dos, se impidió o curó ésta. No pudieron descubrirse signos histológicos de ningún efecto tóxico de la droga, con la posible excepción de lesiones de los tubérculos renales en un caso. Estas observaciones aportan nuevos datos alentadores acerca de la eficacia terapéutica de la estreptomicina en la tuberculosis y también ofrecen alguna esperanza en cuanto al tratamiento efectivo de dos formas hasta ahora constantemente letales de la enfermedad.

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TUBERCULOSIS IN A LABORATORY MONKEY COLONY[1]

Its Spread and Its Control

KARL HABEL

Tuberculosis has long been recognized as a major cause of naturally occurring deaths in monkey colonies. Because the high incidence of tuberculosis makes these animals of questionable value in certain types of experimental work and because of the war-time scarcity of monkeys, a study of the spread and control of tuberculosis among the *Macacus mulatta* monkeys housed at the National Institute of Health was begun in January 1942. This report presents the findings of the first three years of study.

METHODS

Physical arrangements for care of monkeys: A separate building is used for housing groups of monkeys, both those of fresh stock and those discharged after being used experimentally. This building is divided into four large rooms, each with an open-faced shelter and a wire-enclosed runway. The rooms and shelters are divided by walls lined with sheet metal, and the runways are separated by two layers of composition board so that no intimate contact between groups is possible. Monkeys in each room are fed and watered from common receptacles. Food trays are cleaned daily, and rooms and runways are thoroughly cleaned with hot water every two weeks. Monkeys withdrawn from the colony for experimental use are taken to small laboratory rooms in another building and are kept in cages, either separately or at most 2 to a cage.

The personnel handling and feeding the monkeys is limited to three persons, all of whom have a roentgenogram of the chest every six months because of their possible exposure to tuberculosis; their roentgenograms have remained negative for evidence of pulmonary tuberculosis. Monkeys withdrawn from the colony for experimental use come in contact with a relatively large number of persons. A recent X-ray survey of all personnel in the Institute revealed no infectious cases in any of the scientific personnel or attendants.

Normal flow of monkey population in the Institute: Newly acquired monkeys after release from a quarantine room are kept in one of the rooms of the monkey house (room 1, 2 or 3 in chart 1). Monkeys newly purchased from dealers are kept together—in room 1 or room 2 without further additions until all have been used for experimental purposes. Room 3 houses newly acquired monkeys from a branch laboratory and frequently receives additional monkeys. The monkeys in rooms 1 and 2 could not be identified separately whereas those in room 3 were already tattooed with numbers when received. Most of the stock monkeys were kept in the colony for at least six months before issue and during that time there were deaths from natural causes.

[1] From the Division of Infectious Diseases, National Institute of Health, Bethesda Maryland.

When taken from the colony for experimental use, monkeys were tagged or tattooed with an identifying number and were taken to various laboratory rooms

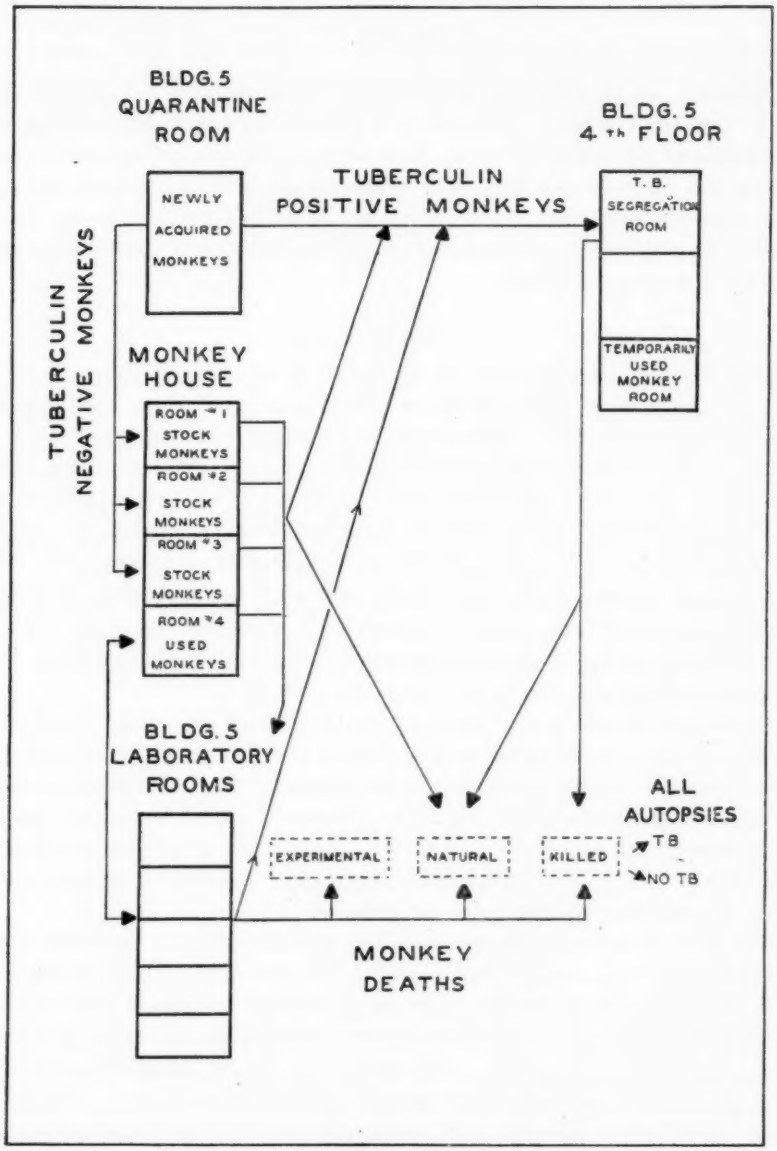

CHART 1. Flow of monkey population in National Institute of Health.

in Building 5. These animals usually were on experiment for a relatively long time (several months), and during that time there were deaths due to experimental and natural causes. Many also were sacrificed during the course of experi-

ments. Those that survived were returned to room 4 in the monkey house so that this room received frequent additions of a few used animals from the laboratory rooms of Building 5. On two occasions during the study, because of crowding in room 4, it was necessary to keep some of our used monkeys in a room on the fourth floor of Building 5. This temporary room was separated from the tuberculosis segregation room by several rooms and a corridor but was on the same floor. Used monkeys are frequently reissued to the laboratory building.

Tuberculin testing: A single lot of Old Tuberculin, prepared for veterinary use (B.A.I. lot No. 782) was used. Immediately prior to use, it was diluted with physiological saline so that 0.1 cc. contained 5 mg. of OT. This amount was injected intracutaneously into the right upper eyelid. Readings were made at the end of forty-eight hours. A positive reading was based on edema of the upper eyelid as evidenced by thickening and narrowing of the palpebral opening. Redness alone was not considered a positive reaction. No attempt was made to grade the degree of positivity.

Method of segregation of monkeys according to tuberculin reaction: All monkeys in the Institute, both fresh and used, were tuberculin tested at the beginning of the study. The tuberculin-positive animals were removed and kept in cages in a separate room on the fourth floor of Building 5 until they died or were killed.

Newly acquired monkeys when received at the Institute were placed in isolation, 2 or 3 to a cage, in a quarantine room in Building 5. These new monkeys were then tuberculin tested and all reactors removed to the tuberculosis segregation room. For the period October, 1941 to October, 1943 a single test was performed and the negative reactors immediately introduced into room 1, 2 or 3 of the colony. Since October, 1943 all new monkeys have been tested when received but kept in the quarantine room for one month, when they were retested. Only the negative reactors to both tests were added to the colony.

All monkeys, including stock monkeys in the colony, those on experiment and used monkeys were then tested at regular intervals; the reactors were removed to the tuberculosis segregation room. This routine testing of all monkeys was done at six-month intervals for the first year of the study and at three-month intervals after that time.

Diagnosis of tuberculosis: Autopsies were performed with few exceptions on all monkeys killed or dying during the study period. The diagnosis of tuberculosis in all instances was based on the gross finding of tubercles or caseation in the lungs, pleura, pericardium, hilar nodes, liver, spleen, kidney, intestines, peritoneum, mesenteric nodes, bladder, ovary, testicle or retroperitoneal nodes.

INCIDENCE OF TUBERCULIN SENSITIVITY IN MONKEYS

Results of tuberculin tests in monkeys at beginning of study: Monkeys kept for varying periods up to several years without any segregation of tuberculous animals were all tested at the start of the study. Of 183 such monkeys, 71 (or 39 per cent) were tuberculin-positive.

Results of tuberculin tests according to the source of animals entering the colony: In table 1 are listed the tuberculin reactions of different groups of monkeys enter-

ing the colony directly from shipboard, after various lengths of stay in an animal dealer's colony, and after having been used experimentally in a branch laboratory in a different part of the country. These reactions may be compared with the reactions of the fresh stock and used monkeys already at the Institute at the

TABLE 1

Results of tuberculin tests according to source of monkeys

	TOTAL NUMBER OF MONKEYS	TUBERCULIN-POSITIVE	
		Number	Per cent
Direct from shipboard	123	4	3
Indirect, through dealer	392	90	23
Indirect, from branch laboratory	377	97	26

TABLE 2

Total incidence of tuberculin reactors and tuberculosis in all monkeys while housed in the Institute

TIME INTERVAL	TOTAL NUMBER OF MONKEYS*	NEW TUBERCULIN POSITIVES		AUTOPSY FINDINGS†			NONTUBERCULOUS DEATHS‡	PERCENTAGE LOSS	
		Number	Per cent	Tuberculous	Nontuberculous	Per cent tuberculous		Tuberculous§	Nontuberculous‖
Jan. to Mar. 1942	140			12	21	36	12	9	9
April to June 1942	140	12	9	31	22	58	10	22	7
July to Sept. 1942	162	6	4	41	16	72	5	25	3
Oct. to Dec. 1942	270	25	9	46	25	65	10	17	4
Jan. to Mar. 1943	211	11	5	30	31	49	17	14	8
April to June 1943	213	19	9	14	7	66	4	7	2
July to Sept. 1943	181	2	1	28	15	65	8	15	4
Oct. to Dec. 1943	159	2	1	10	13	43	5	6	3
Jan. to Mar. 1944	166	6	4	12	19	39	11	7	7
April to June 1944	178	2	1	24	10	70	7	14	4
July to Sept. 1944	150	11	7	16	14	53	10	11	7
Oct. to Dec. 1944	165	5	3	26	17	60	14	16	8
Total three years ..		101	14	290	210	58	113	33	13

* Tuberculin-negative on previous tests.

† All monkey deaths "natural and experimental."

‡ Naturally occurring nontuberculous deaths.

§ Effective loss due to tuberculosis = 100 × (number showing tuberculosis at autopsy)/(total number of monkeys).

‖ Effective loss from nontuberculous causes = 100 × (number of naturally occurring nontuberculous deaths)/(total number of monkeys).

beginning of the study. From these results it would appear that the tuberculin-reactor rate in monkeys is relatively low on arrival in this country and that the longer the monkeys have been housed together without segregation of tuberculous animals the higher the rate. Of a total of 892 new monkeys received, 701 were tuberculin-negative on arrival.

Total incidence of tuberculin reactors and tuberculosis at autopsy in monkeys while housed at the Institute: Table 2 indicates the total number (arranged by three-month periods) of originally tuberculin-negative monkeys on hand, the number having a positive reaction, the number killed or dying with tuberculosis proved at autopsy and the number of nontuberculous deaths during the course of the study.

From this table it is apparent that tuberculosis represents the chief cause of natually occurring loss in our monkey colony, as one third of all monkeys received at the Institute had or developed the disease over a three-year period. Of the monkeys tuberculin-negative when received, 14 per cent subsequently became tuberculin-positive. The rate of new positive reactors at three-month intervals varied from 1 to 9 per cent; the rate was not appreciably reduced during the period of study. This of itself would indicate that the control of tuberculosis in the colony has not been accomplished by our method of segregation of reactors. However, the true picture is obtained by a break-down of all the monkeys in the Institute into the isolated groups composing the total reported.

Development of tuberculin reactivity in fresh stock monkeys: In table 3 are listed the new monkeys added to the stock colony (rooms 1, 2 and 3) with the incidence of tuberculin reactions in each group before their introduction. The amount of reactivity of the entire fresh stock colony is also given for each three-month interval. The incidence of reactors in monkeys before introduction into the colony varied from 0 to 60 per cent, but considering the whole number of monkeys added each year it was relatively uniform from year to year. The incidence of reactors in the fresh stock colony itself varied from 0 to 42 per cent but decreased as the study progressed so that not a single tuberculin reactor was found in the last eighteen months of observation.

Here again a break-down of results by separate rooms gives a clearer picture of the spread of tuberculosis among these fresh stock monkeys. As mentioned under "Methods," two rooms had a homogeneous population during the period of study. Tables 4 and 5 show rooms 1 and 2 in which large groups of tuberculin-negative monkeys were placed without further additions. In room 1, there were 11 per cent reactors on arrival and in room 2, 9 per cent. Monkeys were being continually removed for experimental purposes, but the record of new reactors at three-month intervals in each room shows wide differences. In room 1, all the monkeys remaining in the room had become positive within nine months in spite of the removal of reactors every three months. In room 2, one monkey was positive at six months and 2 at twelve months after their arrival, but none have reacted in the last eighteen months of observation. Tables 4 and 5 include the complete tuberculosis experience of the stock monkeys from rooms 1 and 2 for the first six months after their removal from these rooms for experimental use. This subsequent experience confirmed the earlier experience in the same rooms.

Development of tuberculin reactivity in caged monkeys during experimental use: Table 6 shows the percentage of reactors in monkeys kept in cages in laboratory rooms for varying periods. These monkeys originally came from tuberculin-negative unused stock kept in the monkey house but were tested while on experi-

ments of various kinds. The figures do not include monkeys kept caged in the temporary used-monkey room on the fourth floor of Building 5.

The rates of reactivity varied from 0 to 43 per cent and in general tended to be lower as the study progressed.

Development of tuberculin reactivity in used monkeys: Monkeys after experimental use were kept in room 4 in the monkey house. Eventually most of them were used again for experiments and then killed. The rate of reactors in this

TABLE 3

Development of tuberculin reactivity in stock monkeys

DATE OF TESTS	NEW MONKEY GROUPS BEFORE INTRODUCTION INTO COLONY						MONKEYS IN COLONY		
	First test			Second test					
	Number tested	Number positive	Per cent positive	Number tested	Number positive	Per cent positive	Number tested	Number positive	Per cent positive
10/10/41							111	47	42
1/27/42							66	26	39
1/30/42	88	11	12						
3/23/42	123	4	3						
7/15/42	131	23	18				149	10	7
10/21/42	90	10	11				117	1	1
12/ 1/42	8	1	12						
1/16/43	22	0	0				168	4	2
2/13/43	28	7	25						
4/ 7/43	20	8	40				162	7	4
5/26/43	13	2	15						
6/19/43	17	4	23						
7/ 2/43							130	6	5
9/10/43	15	1	7						
10/ 1/43							177	0	0
12/ 8/43	46	10	22	36	4	11			
1/10/44							66	0	0
2/12/44	28	4	14	24	10	42			
4/ 5/44	13	0	0	13	0	0	57	0	0
5/29/44	24	2	8	22	0	0			
7/12/44							59	0	0
8/ 6/44	21	7	33	14	2	14			
9/15/44	10	6	60	4	0	0			
10/21/44							65	0	0
1/19/45							65	0	0

room varied from 0 to 7 per cent with relatively even distribution throughout the study period, as shown in table 7.

Development of tuberculin reactivity in monkeys kept in cages on the same floor as tuberculous monkeys: A number of used monkeys were kept in cages in the temporary used-monkey room on the fourth floor of Building 5, separate from the room containing the tuberculin-positive monkeys. In table 8 are found rates for the tuberculin-positive monkeys. In three of the five tests the rate was about 25 per cent, but in two tests it was 0. The lack of reactors in these two tests is

TABLE 4

Results of successive tests and subsequent tuberculosis experience of stock monkeys in Room 1

TIME OF TEST	MONKEYS TESTED	TUBERCULIN POSITIVES REMOVED		DEATHS IN COLONY		REMOVALS FOR EXPERIMENT	THREE MONTHS FROM REMOVAL						SIX MONTHS FROM REMOVAL					
							Deaths		Sacrificed		Tuberculin reaction		Deaths		Sacrificed		Tuberculin reaction	
		Number	Per cent	Tuberculous	Nontuberculous		Tuberculous	Nontuberculous	Tuberculous	Nontuberculous	Positive	Negative	Tuberculous	Nontuberculous	Tuberculous	Nontuberculous	Positive	Negative
Before entering colony	97	11	11	0	3	36	1	0	0	4	6	25	4	0	0	4	2	15
3 months after entering colony	47	3	6	0	2	6	0	0	0	1	0	5	0	0	0	0	1	4
6 months after entering colony	36	5	14	0	2	12	0	0	0	0	12	0						
9 months after entering colony	17	17	100															

TABLE 5

Results of successive tests and subsequent tuberculosis experience of stock monkeys in Room 2

TIME OF TEST	MONKEYS TESTED	TUBERCULIN POSITIVES REMOVED		DEATHS IN COLONY		REMOVALS FOR EXPERIMENT	THREE MONTHS FROM REMOVAL						SIX MONTHS FROM REMOVAL					
							Deaths		Killed		Tuberculin reaction		Deaths		Killed		Tuberculin reaction	
		Number	Per cent	Tuberculous	Nontuberculous		Tuberculous	Nontuberculous	Tuberculous	Nontuberculous	Positive	Negative	Tuberculous	Nontuberculous	Tuberculous	Nontuberculous	Positive	Negative
Before entering colony*	104	10	9	0	0	0												
3 months after entering colony	67	0	0	0	2	0												
6 months after entering colony	65	1	2	0	0	3	0	0	0	0	0	3	0	0	0	0	0	3
9 months after entering colony	61	0	0	0	1	0												
12 months after entering colony	60	2	3	0	0	12	0	1	0	2	0	9	0	0	0	1	0	8
15 months after entering colony	46	0	0	0	2	1	0	0	0	1	0	0						
18 months after entering colony	43	0	0	0	2	2	0	0	0	1	0	1	0	0	0	0	0	1
21 months after entering colony	39	0	0	0	2	10	0	0	0	1	0	9	0	1	0	0	0	8
24 months after entering colony	27	0	0	0	2	2	0	1	0	0	0	1	0	0	0	0	0	1
27 months after entering colony	23	0	0	0	2	0												
30 months after entering colony	21	0	0															

* 104 purchased as group but only 67 placed in Room 2.

explained by the fact that one of the groups was kept in this room less than three months and the second group had been placed in the room just before the test (July 12, 1944) but subsequently developed a high rate (October 20, 1944).

TABLE 6

Results of successive tuberculin tests in caged monkeys during experimental use

DATE TESTED	NUMBER TESTED	TUBERCULIN-POSITIVE	
		Number	Per cent
10/22/42	45	5	11
1/13/43	28	4	14
4/ 7/43	25	4	16
7/ 1/43	28	12	43
10/ 1/43	27	1	4
1/12/44	23	1	4
4/ 5/44	36	0	0
7/26/44	34	0	0
10/20/44	42	2	5
1/17/45	37	0	0

TABLE 7

Results of successive tuberculin tests in used monkeys kept in a group

DATE TESTED	NUMBER OF MONKEYS	TUBERCULIN-POSITIVE	
		Number	Per cent
4/ 8/43	24	2	4
7/ 1/43	33	0	0
10/ 1/43	38	1	3
1/19/44	30	0	0
4/ 5/44	23	0	0
7/26/44	30	2	7
10/21/44	42	3	7
1/24/45	41	0	0

TABLE 8

Results of successive tuberculin tests on monkeys kept caged on same floor as tuberculous monkeys

DATE TESTED	NUMBER OF MONKEYS	TUBERCULIN-POSITIVE	
		Number	Per cent
1/13/43	72	17	24
10/ 1/43	39	0	0
7/12/44	55	0	0
10/20/44	26	6	23
1/17/45	22	5	23

Development of tuberculin reactivity in a group of monkeys introduced in the tuberculosis room: For experimental purposes a group of 23 used monkeys that

had been tuberculin-negative for at least six months and had not been exposed to any positive monkeys for the same period were introduced in the room containing about an equal number of tuberculin-positive animals. The tuberculin-positive monkeys were in various stages of the disease, many with far advanced symptoms and were in cages at one end of a large (16 by 32 feet) low-ceilinged room with two windows, one door and one ventilation vent to the outside. The negative reactors were in cages at the opposite end of the room; the latter monkeys were fed and their cages cleaned first, but no special precautions were taken against dust or air flow in ventilation.

As can be seen in table 9, at the end of three months 18 per cent of the negative monkeys had become positive or had died of tuberculosis; at the end of six months, 57 per cent; after nine months, all were tuberculous.

TABLE 9

Spread of tuberculosis from tuberculin-positive to tuberculin-negative monkeys housed in one room

DATE	TUBERCULIN TEST			DEATHS			PER CENT OF MONKEYS DEVELOPING TUBERCULOSIS†
				Tuberculosis at autopsy			
	Number tested	Number positive	Per cent positive	Previously tuberculin-positive	Previously tuberculin-negative	Nontuberculous	
4/ 5/44*	23	0	0				
7/13/44	21	3	14	0	1	1	18
10/20/44	17	8	47	2	0	1	57
1/17/45	5	5	100	6	3	1	100

* Date introduced into room—not exposed to tuberculosis for six months.

† Per cent either tuberculin-positive or dead of tuberculosis after eliminating the nontuberculous deaths.

THE CONTROL OF SPREAD OF TUBERCULOSIS IN THE MONKEY POPULATION

Table 3 lists the results of tests in new groups of monkeys added to the colony and the effect on the rate in the colony at three-month intervals. After the initial high rates, the incidence of reactors in the colony settled down to about 5 per cent no matter what the rates in the groups had been before their introduction. However, beginning in October, 1943, a change was made in the testing of newly arrived monkeys. Instead of testing once and then adding all negative animals to the colony, all new monkeys were kept isolated for one month and tested twice, the tests being one month apart. After two negative tests the monkeys were added to the colony. Of a total of 142 newly arrived monkeys thus tested, 29, or 20 per cent, were positive on the first test. Of 113 originally negative, 16, or 14 per cent, were positive one month later. Of 10 monkeys negative on both tests but subsequently positive, 7 had been exposed during quarantine to a positive animal in the same cage. The positive reactions in these 7 developed during further isolation. The other 3 became positive three, three and nine months,

respectively, after their second original negative test, although their only exposure had been during shipment.

With this change in the routine testing of newly acquired monkeys, no further reactors were found in the colony over a period of eighteen months. At the same time this decrease in reactors in the fresh-stock colony was reflected in the rates of the animals on experiment and, to some extent, in the rates of the used-monkey group.[2]

However, during this same period the rate of reactors in the monkeys in the temporary room of the fourth floor of Building 5 was 23 per cent. This particular group had indirect exposure to the tuberculin-positive group because they were housed on the same floor. The rate in those exposed more directly by being caged in the same room with the reactors had reached 100 per cent at the same time.

Another indication of the effectiveness of the method of control is the difference in the total incidence of tuberculin reactors at the beginning and at the end

TABLE 10

Total incidence of tuberculin reactors in Institute at start and end of study period

DATE	NUMBER OF MONKEYS	TUBERCULIN-POSITIVE	
		Number	Per cent
1/27/42	184	73	40
1/17/45	165	23	14

of the study period including all monkeys alive at the time. Table 10 shows that the drop was from 40 to 14 per cent.

CORRELATION OF TUBERCULIN TEST RESULTS AND SUBSEQUENT AUTOPSY FINDINGS

Monkeys employed in this study either died or were killed at various intervals following the tuberculin tests. Gross evidence of tuberculosis at autopsy was then checked against the last test performed on the animal in relation to the time interval from test to autopsy. In table 11 are shown the results of tuberculin tests of 503 monkeys which had been tested at least once. The degree of correlation was high when the tuberculin test was positive no matter how long the interval between test and autopsy. However, in the case of tuberculin-negative animals, the degree of correlation decreased as this interval became longer. In other words, the chances of an animal's becoming infected with tuberculosis increased with the length of his stay in the colony. After a lapse of three months from the last test it will be practically impossible to evaluate the tuberculosis situation in the colony.

Since many of the monkeys included in table 11 were tuberculin-positive on arrival and no information was available as to their previous status concerning

[2] Since preparation of this manuscript an additional twenty-four months' observation has been completed, and no reactors were found in any of the monkey groups in the Institute.

tuberculosis, table 12 includes only those animals which had become reactors following at least one negative test. Here the correlation is 100 per cent in 110 animals no matter what the intervals from test to autopsy.

TABLE 11

Correlation of tuberculin test results and autopsy evidence of tuberculosis according to interval from test to autopsy

INTERVAL FROM TEST TO AUTOPSY	TUBERCULIN-NEGATIVE		PER CENT CORRELATION	TUBERCULIN-POSITIVE		PER CENT CORRELATION	TOTAL PER CENT CORRELATION
	Autopsy negative	Autopsy positive		Autopsy positive	Autopsy negative		
Under one month	85	8	91	56	4	93	92
One to two months	66	12	85	45	1	98	89
Two to three months	49	13	79	39	0	100	87
Over three months	17	42	29	64	2	97	65
Totals....	217	75	74	204	7	96	84

TABLE 12

Correlation of tuberculin test results and autopsy evidence of tuberculosis in monkeys becoming tuberculin-positive in the colony

INTERVAL TEST OF AUTOPSY	TUBERCULIN-POSITIVE	
	Autopsy positive	Autopsy negative
Under one month	33	0
One to two months	23	0
Two to three months	28	0
Three to six months	16	0
Six to twelve months	7	0
Over twelve months	3	0
Total.....	110	0

TIME OF DEATH OF MONKEYS AFTER BECOMING TUBERCULIN-POSITIVE

Chart 2 shows the time of death of monkeys following their first positive tuberculin reaction. All these animals had been tuberculin-negative three months before becoming positive. The time of death varied from one to fifty-eight weeks after a positive test; 35 per cent were dead by the end of six weeks; 71 per cent by the end of twelve weeks; 85 per cent after sixteen weeks.

In this study, all tuberculin-positive monkeys developed severe symptoms and

died within less than fifty-eight weeks no matter what size or age. It was also observed that young monkeys under one year of age and pregnant monkeys

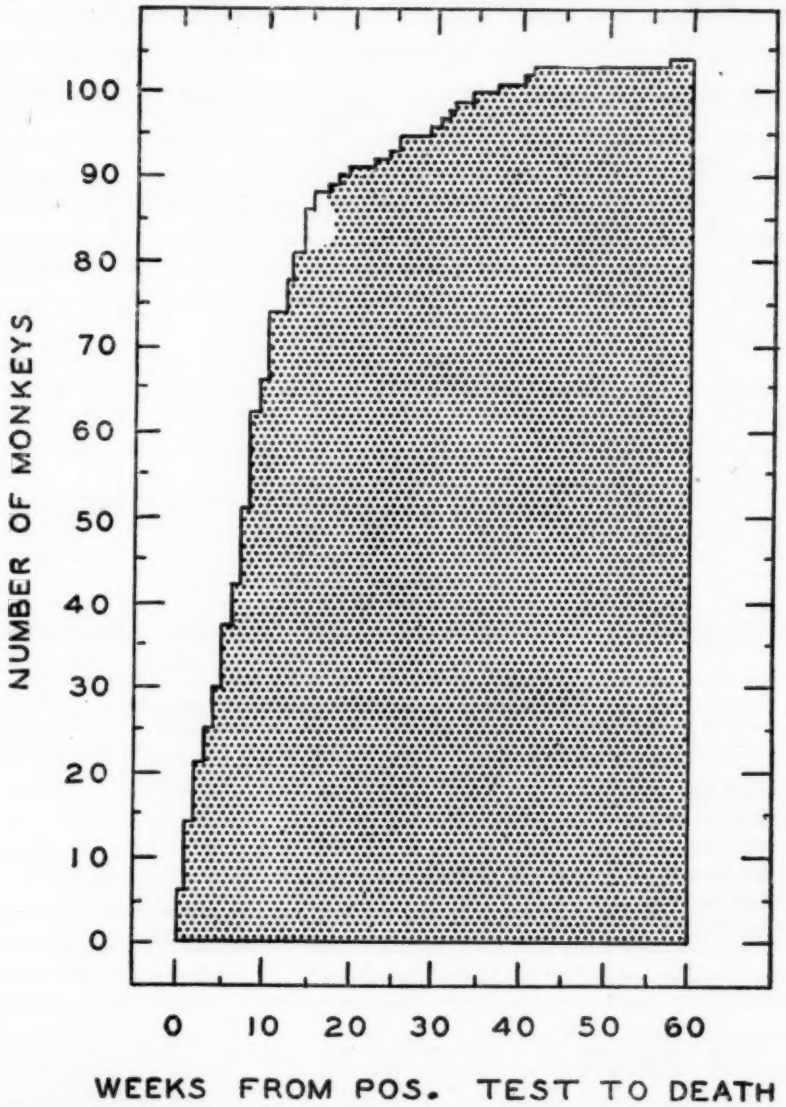

CHART 2. Time of death after becoming tuberculin-positive in 104 monkeys which were tuberculin-negative three months previously.

developed severe symptoms and died more rapidly than did the average monkey.

When the same tabulation was made for 16 monkeys that became tuberculin-positive one month after a negative reaction, the time of death varied from one

to thirty-two weeks, with 19 per cent dead at the end of six weeks; 44 per cent by twelve weeks; 62 per cent by sixteen weeks; 75 per cent by twenty weeks. (See chart 3.)

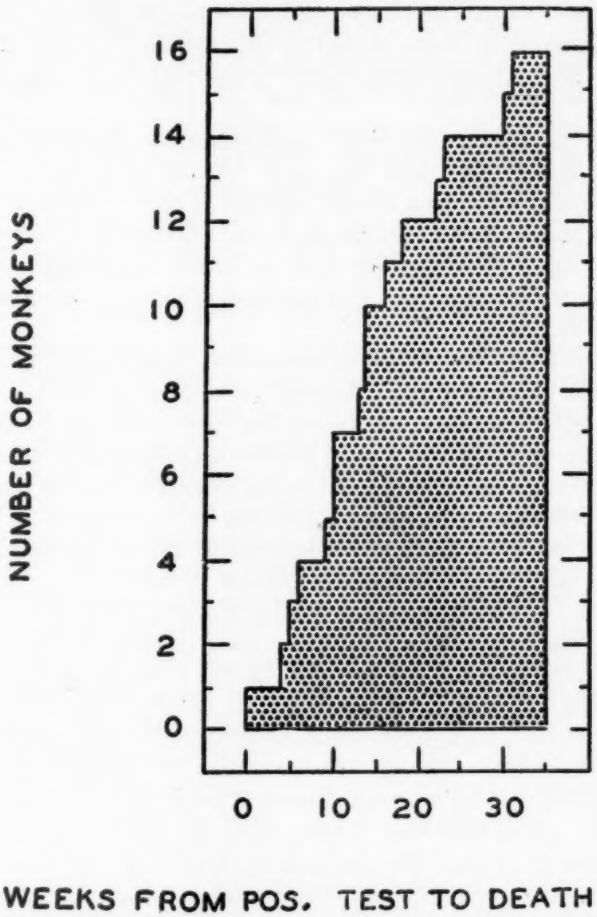

CHART 3. Time of death after becoming tuberculin-positive in 16 monkeys which were tuberculin-negative one month previously.

DISCUSSION

White and Fox (1) in 1909 were the first to report the use of tuberculin reactions as a means of diagnosing tuberculosis in primates. They used the temperature reaction following subcutaneously administered Old Tuberculin (1 to 2 mg.) for determining a positive test. Of 81 negative reactors they reported a total of 10 deaths due to tuberculosis. One of the animals died one month after the test, but the rest were autopsied three months or more after the last test. Of 56 reactors, 41 had tuberculosis at autopsy, but 15 had not. White

and Fox found the average exhibition life of monkeys at the Philadelphia Zoo to be eleven months before testing and segregation and thirty-five months after seventeen years of such testing. Before testing, 78 per cent of all deaths were from tuberculosis. In the first four years after beginning the testing and segregation, there were only 2 deaths caused by tuberculosis but those 2 were followed by 13 more in the following three years. After that there were only scattered cases.

Schroeder (2) was the first to use the eyelid as the site of injection for the tuberculin test in monkeys, and later Kennard, Schroeder, Trask and Paul (3) reported on the eyelid test using Old Tuberculin (1 mg.). They found a correlalation between postive test and autopsy in 45, negative test and autopsy in 62, a negative test with positive autopsy in 9, and positive test with negative autopsy in 4. However, there was no record of the lapse of time between test and autopsy on these monkeys.

In the present study the degree of correlation between test and autopsy was 93 per cent or more in all tuberculin-positive animals no matter what the time interval from test to autopsy. Likewise the correlation was 91 per cent in tuberculin-negative animals if autopsied within one month of being tested. However, the longer the monkey exposed to tuberculous animals remained in the colony after the last negative test, the less was the correlation.

Some idea of the time involved in developing tuberculin sensitivity may be obtained from this break-down of correlation in tuberculin-negative monkeys after one month. Further evidence is also afforded by the fact that in spite of removing reactors every three months in some rooms, tuberculosis continued to spread. Finally there is the fact that of 123 monkeys exposed during shipment, but found to be negative on arrival, 16, or 13 per cent, were positive one month later. These data suggest that tuberculin sensitivity develops in monkeys within a month or less after infection and that by the time the monkeys are tuberculin-positive they have gross evidence of the disease when autopsied.

Many monkeys that have been in the colony for two to three years have been repeatedly tuberculin tested, the injection always being made in the same eyelid, yet there has been no evidence of development of sensitivity as a result of the repeated testing alone.

Macacus mulatta monkeys are apparently very susceptible to tuberculosis spread through the type of contact obtaining in a monkey colony. If exposed long enough (see tables 4 and 9), all develop the disease and, once having been infected to the point of having a positive tuberculin test, they all die, usually within six months. Thus far in our experience, no reactor has lived longer than fifty-eight weeks. Repeated subinfective exposures to other tuberculous animals apparently does not produce any amount of resistance as the incidence of tuberculosis in old monkeys on hand from the start of the study was no less than in new animals.

The mode of spread of tuberculosis was not clearly apparent until the exposure shown in tables 8 and 9 was observed. In these two groups, because opportunity for direct contact or transfer by food was minimal, air-borne or dust-borne infections seemed more likely.

From the experience presented herein, it is apparent that the spread of the disease in a monkey colony depends first on the degree of contact with a tuberculous monkey at the time the animal is eliminating organisms either in the stool or expired air. This is shown by the rates of reactors which increase progressively from the lowest rate to the highest in the following order: (*1*) animals exposed in rooms where all reactors were removed every three months, (*2*) those in rooms on the same floor as the tuberculous animals, (*3*) those in the room containing tuberculous monkeys, (*4*) animals in the same cage with a tuberculous monkey. The length of contact with a tuberculous monkey is also a factor as shown in the original rates of newly acquired animals and those kept together for long periods at the beginning of the study. The proportion of diseased animals in any group for a given period of time, as would be expected, also determined the secondary rates as indicated in those groups double-tested on arrival (table 3).

The rapidity of spread of tuberculosis in a colony can be estimated from the results in the tuberculosis room where at the end of three months 18 per cent of negative monkeys were infected, at six months 57 per cent and at nine months 100 per cent. In room 2 where reactors were being removed at three-month intervals only nine months were required for all to be infected.

From the results presented here, it would appear that the control of tuberculosis in a monkey colony can be accomplished by tuberculin testing and removal of reactors. Complete segregation or destruction of these reactors would seem indicated, since they are a constant source of infection to other monkeys in close proximity, even in separate rooms, and all will eventually die of their tuberculosis. The ideal method of control would seem to be isolation of new monkeys; two negative tuberculin tests one month apart before they are added to the colony; all the negative reactors which have been kept in cages with positively reacting monkeys during their segregation to be isolated further. An additional precaution in maintaining control would be to keep the large groups of fresh stock animals as homogeneous as possible, using all in a room before adding more. In the established colony, routine tests every three months are indicated. If the disease spreads in spite of this removal of reactors every three months, testing should be done monthly until control is established. In a homogeneous group, if three successive tests at three-month intervals have been completely negative, tests may be spaced at six-month intervals.

The material reported here justifies the use of *Macacus mulatta* monkeys in epidemiological and immunological studies of the spread of tuberculosis in experimental animals.

SUMMARY

1. Tuberculosis is the chief cause of naturally occurring deaths in this monkey colony of *Macacus mulatta*.

2. The incidence of tuberculosis and its spread in a monkey colony depend on the degree of contact, length of contact and density of infected animals.

3. Spread is probably through the respiratory tract.

4. In *Macacus mulatta* monkeys tuberculosis is a fatal disease and there is no evidence of immunity.

5. The spread of the disease in the colony can be controlled by repeated tuberculin testing with removal of reactors.

6. A high degree of correlation between tuberculin test and autopsy evidence of tuberculosis is demonstrated.

7. The majority of monkeys die of tuberculosis within six months of their becoming tuberculin-positive.

SUMARIO

1. La tuberculosis es la principal causa de la mortalidad natural en la colonia de monos *Macacus mulatta* estudiada.

2. La incidencia de la tuberculosis y su propagación en una colonia de monos dependen de la intensidad y duración del contacto y la densidad de los animales infectados.

3. La propagación tiene lugar probablemente por vía respiratoria.

4. En los *Macacus mulatta* la tuberculosis es una enfermedad letal, sin que se observen signos de inmunidad.

5. La propagación de la dolencia en la colonia puede cohibirse mediante la repetida comprobación con tuberculina y la eliminación de los reactores.

6. Queda demostrada la intensa correlación entre el resultado de las pruebas con tuberculina y los hallazgos autópsicos de tuberculosis.

7. La mayoría de los monos mueren de tuberculosis en un plazo de seis meses después de volverse positivos a la tuberculina.

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TUBERCULOSIS IN THE ALABAMA STATE HOSPITALS

Mass Radiography for Its Control

A. H. RUSSAKOFF[1,2]

It has been recognized for many years that the prevalence of tuberculosis among mentally ill patients is exceedingly high. Weber, Plunkett and McCurdy (1) reported that during the years 1939 to 1941 the tuberculosis death rate among patients of 26 institutions for the mentally ill and defective in New York State was 593.6 as compared to 46.8 for the State as a whole. Thus, 0.6 per cent of the population accounted for 8.1 per cent of all reported tuberculosis deaths. X-ray examinations of the patients in 20 hospitals in the State disclosed that 4.7 per cent of the patients had lesions of clinical significance and an additional 4.6 per cent had lesions which were considered to be apparently healed. Hilleboe (2) reported that of 6,446 newly admitted patients to hospitals for the insane in Minnesota during the years 1936 to 1939, inclusive, 5.3 per cent of the males and 5.8 per cent of the females were found to have tuberculous lesions demonstrated by routine X-ray examinations of the chest. His study also disclosed the prevalence of tuberculosis to be highest among persons 65 years of age and over. Pollack, Hummell and Turow (3) reported that 11.2 per cent of resident patients, 5.7 per cent of new admissions and 1.6 per cent of the employees at the Peoria State Hospital had tuberculous lesions found by radiography of the chest. Their study indicates also that the tenure of hospitalization is a factor in the development of the disease. It is significant that approximately 80 per cent of those persons who developed tuberculosis in that institution did so after a resident period of five or more years.

Late in 1944, the writer directed an X-ray study of the patients in an institution for the mentally ill in another state which previously had reported an exceedingly low prevalence of tuberculosis. Reference to this institution's supposedly unusual record appears in one of the well-known volumes on clinical tuberculosis (4). Results of this radiographic study disclosed the prevalence of tuberculosis (active and inactive) among the presumably well patients alone, exclusive of known cases, to be slightly in excess of 10 per cent (5). These findings are presented only to demonstrate once again that the prevalence of tuberculosis in any given community cannot actually be defined without radiography of all persons.

Since it has been the experience in practically all institutions for the mentally ill in this country, where mass radiography has been carried out, that these hospitals are virtually repositories of tuberculosis, arrangements were made in the spring of 1945 to X-ray all patients in the State Hospitals in Alabama. The State of Alabama supports 3 institutions for the mentally ill: (*1*) Bryce

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Hospital, predominantly for white patients, in Tuscaloosa, (*2*) Searcy Hospital for colored patients, near Mobile and (*3*) the Partlow State School for the mentally deficient, in Tuscaloosa. (This study does not include the survey at the Partlow State School). Both the Bryce and Searcy Hospitals are old institutions with grossly inadequate facilities for the care of tuberculous patients. The known infectious cases at the Bryce Hospital are segregated by sex in two distantly separated old cottages, both inaccessibly removed from the X-ray facilities. Although chest roentgenograms are not made routinely, patients found to have abnormalities on physical examination at the time of admission and during the period of hospitalization are X-rayed.

At the Searcy Hospital, however, there have been no special provisions for tuberculous patients. Consequently, adequate precautions have not been taken. Although an X-ray machine was installed in the Searcy Hospital more than a year ago, shortages in personnel have made it impossible to utilize this equipment for radiographic examinations of the chest. Neither hospital has a staff physician who has been trained specifically in the treatment of tuberculosis, and no collapse therapy is done.

During the year ending September 30, 1944, pulmonary tuberculosis accounted for 20 deaths (6.1 per cent of reported deaths) at the Bryce Hospital. During the same year, there were 35 deaths due to pulmonary tuberculosis at the Searcy Hospital. These cases represent 11.7 per cent of all deaths for 1944 in that institution. For both hospitals, pulmonary tuberculosis accounted for 8.8 per cent of all deaths (6) . Here, too, as among the population at large, tuberculosis is the number one bacteriological cause of death. Since mass radiography had never been done in these institutions previously,[3] and since few X-ray films of the chest and autopsies were carried out in 1944, it can be assumed that these figures are somewhat lower than will be the case in the future, because many new cases have been discovered which were undiagnosed prior to this study.

Wide-spread experience in mass radiography among supposedly healthy population groups throughout the country has demonstrated conclusively that this is the most dependable means of uncovering cases of tuberculosis in the early stages of the disease at a low per capita cost (7). It is with such cases that the results of treatment are most apt to be favorable. It is most important from the epidemiological viewpoint that the disease process can be checked or the patient isolated permanently, lest he menace the health of persons in his environs. That mass radiography in institutions for the mentally ill would be profitable case-finding projects is attested by the following facts:

1. The death rates indicate that the morbidity should be high.
2. The long period of confinement and necessary crowding is responsible for repeated and prolonged exposure among patients.
3. The fact that depression is so frequently coupled with inadequate nutrition makes for a lowering of the general resistance. The seniles, paretics, arteriosclerotics and withdrawn schizophrenics so frequently exhibit evidence of diminished *vis a tergo* as to include them in this category.

[3] A partial X-ray study was carried out at the Searcy Hospital several years ago.

4. The inability of psychotic patients to interpret and make known their somatic aberrations and the inability of such patients to coöperate during the course of physical examinations and investigative procedures increase the difficulty of arriving at the correct diagnosis of nonpsychiatric medical problems.
5. The fact that the number of physicians, nurses and other trained personnel has been curtailed during the past several years must be reflected in a somewhat lowered standard of medical care.
6. It is an accepted fact that the prevalence of tuberculosis is higher among groups of persons emanating from the lower socio-economic strata of society than among higher income groups. Of 546 patients admitted to the Bryce Hospital in 1944, 408 (74.7 per cent) were classified as arising from marginal and dependent economic circumstances. Of 389 patients admitted to the Searcy Hospital during the same year, 369 (94.9 per cent) were representatives of this low income group (8).
7. Since the prevalence of tuberculosis is highest in the age groups 20 to 45, and since both institutions house adult patients, it might be anticipated that a number of cases of pulmonary tuberculosis would be found in the various age groups represented.
8. The experience of other workers in the field of tuberculosis among mentally ill patients indicates that mass radiography has demonstrated a high prevalence of pulmonary tuberculosis.

Taking all of these facts into consideration, chest X-ray examinations of all ambulatory patients in the Bryce and Searcy Hospitals were undertaken with the consent and coöperation of the authorities for several purposes:

1. The extent of the problem intramurally could be defined.
2. By defining the extent of the current problem, the authorities would have reliable data. This material could well be used for the future planning of adequate facilities for the isolation and treatment of tuberculosis in these hospitals.
3. The transmission of the disease within the confines of these institutions could be prevented by isolating infectious cases. Persons with lesions of undetermined activity could be maintained in "semi-isolation" units until the activity of the lesions could be clarified.
4. Since a certain percentage of patients are furloughed and discharged annually from these institutions, it would be in keeping with our State-wide tuberculosis control program to have previously diagnosed these cases in order that proper precautions might be taken to prevent the spread of the disease in the communities to which these persons return.

This study was carried out using 35 mm. X-ray films. Persons found to have suspicious and definite infiltrations were recalled for a conventional 14 x 17″ film. All films were interpreted by the author.

Although the Bryce Hospital is fundamentally an institution for white patients, there were 373 colored patients separately housed there who were well enough to work. In order to present the results of this study by race, these persons are grouped with the Negro patients at the Searcy Hospital.

ANALYSIS OF THE MATERIAL

1. *White patients:* A total of 3,272 presumably well white patients were X-rayed. Of this group, 1,695 were women and 1,577 were men; 178 persons (5.4 per cent) had radiographic evidence of pulmonary tuberculosis (active and

inactive), 4.4 per cent for women and 6.6 per cent for men. Of these cases, 119 (66.9 per cent) were minimal in extent, 49 (27.5 per cent) were moderately advanced and 10 (5.6 per cent) were far advanced. In addition, there were 25 cases diagnosed as being suspicious for reinfection tuberculosis and an additional

TABLE 1

Pulmonary tuberculosis found among presumably healthy patients, Bryce and Searcy Hospitals, 1945, by sex and race

SEX AND RACE	NUMBER EXAMINED	PULMONARY TUBERCUCULOSIS	
		Number	Per cent
White females	1,695	74	4.4
White males	1,577	104	6.6
Total white	3,272	178	5.4
Colored females	932	22	2.4
Colored males	933	20	2.1
Total colored	1,865	42	2.3
Total group	5,137	220	4.3

TABLE 2

Pulmonary tuberculosis found among patients, Bryce and Searcy Hospitals, 1945, by sex and race*

SEX AND RACE	NUMBER OF PATIENTS	PULMONARY TUBERCULOSIS	
		Number	Per cent
White females	1,716	94	5.5
White males	1,590	116	7.3
Total white	3,306	210	6.4
Colored females	939	29	3.1
Colored males	933	20	2.1
Total colored	1,872	49	2.6
Total group	5,178	259	5.0

* Includes known cases of tuberculosis.

case of incompletely healed primary tuberculosis. Since no follow-up data have been obtained on these cases, all 26 are excluded from this study. (See table 1.)

In addition to those cases discovered during the course of this study, there were 32 cases, 20 females and 12 males, who had been diagnosed previously. In-

cluding these known cases, the over-all prevalence of reinfection tuberculosis for the entire group is 6.4 per cent, 5.5 per cent for females and 7.3 per cent for males. (See table 2.)

The average age of the entire white group examined was 47.1 years, that of females being 48.6 and that of males 45.5 years. The average age of white patients with tuberculosis was 49.4 years, that of females, 53.6 years and that of males, 45.9 years. It is noteworthy that the average age of diseased males was only 0.4 years older than the average age of the total male group, whereas the

TABLE 3

Distribution of 5,178 patients X-rayed and of pulmonary tuberculosis found—Bryce and Searcy Hospitals, 1945—by age group, sex, race

AGE GROUP	WHITE PATIENTS						COLORED PATIENTS					
	Female			Male			Female			Male		
	Number examined	Number of cases found	Per cent	Number examined	Number of cases found	Per cent	Number examined	Number of cases found	Per cent	Number examined	Number of cases found	Per cent
Under 15										3		
15–19	14			25			10			25		
20–24	48	2	4.2	76	3	3.9	38			89	3	3.4
25–29	94	2	2.1	102	4	3.9	90	2	2.2	100	1	1.0
30–34	151	8	5.3	171	15	8.8	93	2	2.2	118	2	1.7
35–39	179	7	3.9	218	19	8.7	146	4	2.7	103	1	1.0
40–44	208	7	3.4	242	23	9.5	104	3	2.9	105	4	3.8
45–49	203	7	3.4	161	11	6.8	137	7	5.1	86	5	5.8
50–54	217	9	4.1	136	9	6.6	93	5	5.4	89	1	1.1
55–59	189	18	9.5	151	9	6.0	68	3	4.4	74		
60–64	158	13	8.2	122	10	8.2	76	2	2.6	61	1	1.6
65–69	115	9	7.8	77	5	6.5	39	1	2.6	41	1	2.4
70–74	85	9	10.6	54	1	1.9	24			25	1	4.0
75–79	35	2	5.7	25	3	12.0	5			10		
80–84	6	1	16.7	14	2	14.3	10					
85–89	5			3			1					
90–94	1			1								
Unknown	8			12	2	16.7	5			4		
Total.....	1,716	94	5.5	1,590	116	7.3	939	29	3.1	933	20	2.1

average age of diseased females was exactly 5.0 years older than the average for the entire female group. (See table 3.)

2. *Colored patients:* A total of 1,865 supposedly well colored patients were X-rayed. Of this group, 932 were females and 933 were males; 42 persons (2.3 per cent) had radiographic evidence of reinfection tuberculosis (active and inactive), 2.4 per cent for females and 2.1 per cent for males. Of these cases 24 (57.1 per cent) were minimal in extent, 13 (31.0 per cent) were moderately advanced and 5 (11.9 per cent) were far advanced. In addition, there were 8 cases diagnosed as suspicious for reinfection tuberculosis and one case of pleurisy

with effusion of undetermined etiology. Since no follow-up data have been obtained on these cases, they, too, have been excluded from this study. (See table 1.) Adding to this group of newly discovered cases 7 cases previously diagnosed (all among females) the over-all prevalence of reinfection tuberculosis for the colored group is 2.6 per cent, 3.1 per cent for women and 2.1 per cent for men. (See table 2.)

The average age of the entire colored group examined was 42.9 years, 44.2 years for women and 41.7 years for men. The average age of colored patients with tuberculosis was 44.3 years, 45.5 years for women and 42.5 years for men. Here again, the average ages of diseased patients are higher than the average for the respective sex groups. (See table 3.)

Table 3 demonstrates the number and per cent of cases of reinfection tuberculosis, according to sex and color. There were several patients grouped as "age unknown." Almost all of them were obviously more than 50 years of age.

TABLE 4

Pulmonary tuberculosis among patients Bryce and Searcy Hospitals, 1945, by race, with 50 years of age as a dividing line

AGE	TOTAL WHITE			TOTAL COLORED		
	Total persons	Total tuberculosis	Per cent tuberculosis	Total persons	Total tuberculosis	Per cent tuberculosis
Under 50	1,892	108	5.7	1,247	34	2.7
Over 50	1,414	102	7.2	625	15	2.4
Total	3,306	210	6.4	1,872	49	2.6

Upon grouping the tuberculous patients by races with a dividing line of 50 years of age, we find the prevalence of tuberculosis to be higher among the older group of white patients (7.4 per cent) than for those in the lower age bracket (3.7 per cent), whereas the prevalence is lower among the older colored patients (2.4 per cent) than among younger ones (2.7 per cent). (See table 4.)

Including the known cases of tuberculosis prior to the time of this study, the over-all prevalence of reinfection tuberculosis is 5.0 per cent.

DISCUSSION

In this study, once again, the prevalence of tuberculosis among the presumably well groups is higher for white than for colored patients, 5.4 per cent and 2.3 per cent, respectively; it is highest among white males (6.6 per cent), next highest among white females (4.4 per cent), third among colored females (2.4 per cent) and lowest among colored males (2.1 per cent). To many, still, it may seem paradoxical that there is this discrepancy between mortality rates and the findings in the race groups disclosed by this study. However, as has been discussed in a previous article (8), and as is the experience of other workers in the field of tuberculosis (9), this finding is closely related to the relative duration of the disease in these various groups.

The age factor is an important consideration in tuberculosis studies (10). Table 3 shows a wide distribution of age groups among patients of both races. However, table 3 shows that there were a significant number of cases of tuberculosis among white patients 65 years of age and over. From table 4 it is noted that a higher incidence of tuberculosis is found among whites over 50 years of age, whereas the incidence is lower among colored persons in the older age bracket. Inspection of the tuberculosis mortality charts for Alabama (chart 1) (11) reveals that the rates increase with advancing age in the case of both white sexes, whereas peaks are followed by sharp downward slopes for colored females at 25 and for colored males at 50 years of age. Thus, the higher incidence of

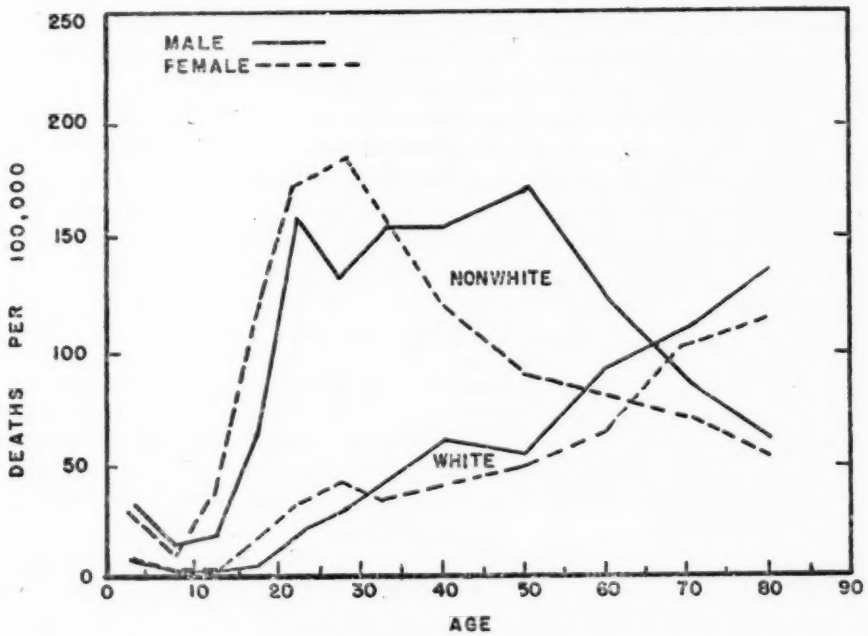

CHART 1. Tuberculosis mortality in Alabama by age. Average annual rate by sex and color, 1939–1941.

tuberculosis among older white patients in this study is quite in keeping with the rising tuberculosis mortality rates for white persons in Alabama as a whole, and the lower prevalence among older colored patients tends to follow the pattern of the mortality curves for the colored persons in this State.

Relative to sex, the incidence of tuberculosis among the supposedly well groups was higher among males of both races combined (4.9 per cent) than among females (3.7 per cent). It is noteworthy that for colored females, which group had the second lowest prevalence, the average of that group as a whole and the average age of tuberculous patients were well beyond the tuberculosis mortality peak. Such was not the case for the other sex-color groups. Accordingly, it would seem that most of the colored females in this study had survived the peak

death period because they had a relative resistance to tuberculosis. In line with the same reasoning, the author cannot explain why colored women did not have the lowest prevalence of tuberculosis in the Alabama State Hospitals.

Although figures have been presented to demonstrate the high percentage of patients in both institutions arising from poor socio-economic circumstances, we do not have available the proportion of tuberculous patients who are representatives of this group. However, since the majority of patients admitted arose from marginal or dependent economic circumstances, it might be anticipated that the figures for tuberculous patients would show the same distribution in general.

It might also be mentioned in passing that a relatively small number of employees and members of their families were X-rayed on a voluntary basis. Of a total of 417 persons examined, 6 previously unknown cases and one known case were found. All but one were among white persons.

Although the results of this study disclose the prevalence of tuberculosis to be lower than that in some other institutions for the mentally ill, it is clear that tuberculosis constitutes a major public health problem among patients and employees alike in the Alabama State Hospitals. The authorities at the Bryce and Searcy Hospitals are to be congratulated on their efforts to cope with the present situation in spite of shortage in personnel, equipment and funds. However, with the cessation of hostilities, the return of personnel and the availability of funds, certain measures should be taken without delay:

1. Adequate provisions should be made for the isolation and treatment of patients with pulmonary tuberculosis at both institutions.[4] These tuberculosis units should be directed by physicians who have been trained in the treatment of tuberculosis. X-ray apparatus should be an integral part of these hospitals, and there should be adequate facilities for doing major chest surgery as well as other types of collapse therapy.
2. All persons admitted to both the Bryce and Searcy Hospitals since the completion of this study should have an X-ray examination of the chest at the earliest possible date, and all patients should be reëxamined immediately prior to discharge, furlough or transfer.
3. It should be required that all personnel have an X-ray examination of the chest as part of the preëmployment physical investigation, and at periodic intervals of not more than one year as long as they remain in the employ of these hospitals. No person with a lesion which is active, or with one of undetermined activity should be employed. Employees with inactive lesions should be X-rayed at intervals of no longer than six months.
4. Mass radiography of all institutions for the metally ill should be repeated every two years. It is noteworthy that reinvestigation elsewhere has been productive of a significant number of cases who were negative on previous examinations.

If this study is to be a worth while contribution, and not merely a survey, it is hoped that the above recommendations can be carried out in the very near future. To do so will not only serve to control tuberculosis in the Alabama

[4] Provisions for providing adequate facilities at Bryce Hospital are now under consideration.

State Hospitals, but will help us sooner to attain our goal—eradication of the disease.

SUMMARY

1. The results of mass radiography for the control of tuberculosis among the patients of two of the Alabama State Hospitals are presented, and the purposes of such investigations have been defined.

2. The findings indicate that pulmonary tuberculosis constitutes a public health problem of major importance.

3. Some of the factors influencing the prevalence of tuberculosis in the various sex, color and age groups have been briefly discussed.

SUMARIO

1. Después de definir los propósitos de tales estudios, preséntase el resultado de la radiografía en masa como arma antituberculosa, en los enfermos de dos de los manicomios del Estado de Alabama, E. U. A.

2. Los hallazgos indican que la tuberculosis pulmonar constituye un problema sanitario de la mayor importancia.

3. Repásanse sucintamente algunos de los factores que afectan la incidencia de la tuberculosis en los varios grupos clasificados conforme a sexo, color y edad.

Acknowledgments

The author wishes to thank Dr. W. D. Partlow, Superintendent of the Alabama State Mental Hospitals, and the staffs of the Bryce and Searcy Hospitals for their interest and cooperation in carrying out this study. Dr. W. D. Partlow made helpful suggestions and made data available to the author. The Alabama Tuberculosis Association made it possible for Mrs. A. H. Russakoff to do the statistical work in this study. Mrs. Parker, Sanitation Division of the Alabama State Health Department, prepared the charts in this study.

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AMERICAN TRUDEAU SOCIETY

Report of the Third Michigan-Wisconsin-Minnesota Regional Therapy Conference

Conference Committee

Dr. John D. Steele, *Chairman*

Dr. Karl H. Pfuetze Dr. John W. Towey

The third annual Michigan-Wisconsin-Minnesota regional conference on tuberculosis therapy was held at the Four Seasons Club near Pembine, Wisconsin, on June 28, 29, and 30, 1946. Forty-eight delegates from the three states were present. In addition, the following physicians were present as observers from other parts of the country: Dr. Kirby S. Howlett, Jr., Shelton, Connecticut; Dr. Paul P. McCain, Sanatorium, North Carolina; Dr. Robert R. Shaw, Dallas, Texas; Dr. Henry C. Sweany, Chicago, Illinois; and Drs. John B. Barnwell and George C. Owen, Veterans' Administration, Washington, D. C.

Morning, afternoon and evening sessions of the first day, and morning and afternoon sessions of the second day were devoted to case presentations. Two four-panel view boxes (furnished through the courtesy of the General Electric X-ray Corporation) were mounted on a raised platform and greatly facilitated the presentation of the roentgenograms.

The case presentations from each state consisted of 20 consecutive patients with thoracoplasty, 20 consecutive patients with pneumothorax (which had been maintained for at least one year) and 20 consecutive patients with phrenic nerve paralysis (for moderately advanced lesions only), making a total of 60 patients for each procedure. The selection of all cases began with January 1, 1943. Each presenter had been instructed to limit his presentation to not more than 8 significant roentgenograms for each case. The date of each film was plainly marked in large numerals. Mimeographed sheets giving significant data on each case were distributed to the audience.

The thoracoplasty patients were presented by Dr. E. Fenger, Glen Lake Sanatorium, Oak Terrace, Minnesota; Dr. Richard H. Schmidt, Jr.,Wisconsin State Sanatorium, Wales, Wisconsin; and Dr. Paul T. Chapman, Herman Kiefer Hospital, Detroit, Michigan.

The pneumothorax patients were presented by Dr. Joseph L. Egle, Northern Michigan Tuberculosis Sanatorium, Gaylord, Michigan; Dr. G. A. Hedberg, Nopeming Sanatorium, Nopeming, Minnesota; and Dr. A. V. Cadden, Muirdale Sanatorium, Wauwatosa, Wisconsin.

The patients with phrenic nerve paralysis were presented by Dr. C. M. Yoran, Rocky Knoll Sanatorium, Plymouth, Wisconsin (10 cases), Dr. L. W. Moody, Pureair Sanatorium, Bayfield, Wisconsin (10 cases); Dr. F. F. Callahan, Minnesota State Sanatorium, Ah-Gwah-Ching, Minnesota (20 cases); and Dr. Edward W. Laboe, Michigan State Sanatorium, Howell, Michigan (20 cases).

The evening session of the second day was devoted to case presentations and

discussion of pulmonary resection for tuberculosis by Dr. Thomas J. Kinsella, Minneapolis, Minnesota and Dr. O. T. Clagett, Rochester, Minnesota.

During the final morning session of the conference, Dr. H. C. Hinshaw, Rochester, Minnesota, presented a detailed discussion of the use of streptomycin in the treatment of tuberculosis. This discussion was accompanied by the presentation of the significant roentgenograms of patients with pulmonary tuberculosis and lantern slides of tuberculous skin lesions which had been treated with streptomycin.

In general, it was felt that the differences of opinion in regard to the choice of therapeutic measures in the treatment of the patients presented were less apparent than they had been during the two previous conferences. The discussion and criticism of the methods of therapy employed were even more free and frank than before, probably because the delegates from the different states had become better acquainted and were not afraid of offending each other by expressing their honest differences of opinion.

It was believed that the patients with specific types of treatment who were presented this year probably did not give as good an indication of the methods of therapy being employed in each state as the consecutive routine admission cases which had been presented at the 1945 conference. However, it was again unanimously agreed that this type of conference was extremely valuable and should be repeated next year by the three states represented.

The mechanics of the case presentations were considered to have been fairly well perfected as the result of the experience of the two previous years.

The following conference committee was appointed to arrange for next year's meeting: Dr. G. A. Hedberg, Chairman, representing Minnesota; Dr. Paul T. Chapman representing Michigan; and Dr. Helen A. Dickie representing Wisconsin.

NATIONAL TUBERCULOSIS ASSOCIATION

Regional Grants for Antituberculosis Work

Financial grants to aid five regions of the United States in meeting serious tuberculosis problems were announced to-day by Dr. Kendall Emerson, managing director of the National Tuberculosis Association. With the hope of improving unfavorable health conditions, the NTA will finance special programs in certain areas of Kentucky, Tennessee, Alabama, Mississippi and Texas which have a high tuberculosis mortality and insufficient organization to cope with the situation.

The NTA has allocated $5000 to each area, to be administered by the local tuberculosis associations in coöperation with state associations and state and local health departments. Professionally qualified staff will be employed for the first time by the local associations, Dr. Emerson said.

The associations chosen to carry out the concentrated programs include the Lauderdale County Tuberculosis Association, Meridian, Mississippi; McCracken County Tuberculosis Association, Paducah, Kentucky; Giles County and Lincoln County Associations, Tennessee; the North Alabama Association, embracing Morgan, Madison and Limestone Counties, Alabama; and Karnes, San Patricio, Live Oak, Wilson and Goliad Counties, Texas.

NOTICE

United States Public Health Service

BCG

Guided by recommendations of a conference of outstanding leaders in tuberculosis from the United States, China, and Denmark, the United States Public Health Service, Federal Security Agency, will extend its tuberculosis research program to include studies on the effectiveness of BCG vaccine in preventing this disease, Surgeon General Thomas Parran announced today.

At the conference, Doctor Herman E. Hilleboe, Chief, Tuberculosis Control Division of the Public Health Service, reviewed the past experience with BCG, named bacillus of Calmette and Guerin for the French scientists who discovered it. Doctor Hilleboe pointed out that the vaccine has been extensively used in Europe and South America in artificial immunization against tuberculosis and that research on this subject has been undertaken in the United States by competent investigators.

From studies presented at the conference, it appears that BCG vaccination confers increased resistance for the limited period covered in these studies but it is not 100% effective. There have been no proved cases of progressive disease resulting from BCG vaccination and it can be used without causing severe local reactions.

Although the conference emphasized that BCG vaccine should not yet be made commercially available in the United States, it strongly advocated extensive research to determine the efficiency of the vaccination. It was also recommended that methods be developed to standardize techniques of preparation of a potent and stable vaccine for use in the United States and if possible throughout the world.

Plans proposed for carrying on this research include: establishment by the Tuberculosis Control Division of a single laboratory to produce BCG vaccine for the entire country for use in research programs; extensive investigations to be carried on coöperatively by recognized research groups throughout the country during the coming years, especially in population groups highly exposed to tuberculosis; controlled study by the Tuberculosis Control Division in a community containing 100,000 or more people to determine immediate and long-range results; development of methods to standardize techniques of preparation of a potent and stable vaccine.

Distinguished men of science attending the conference were Doctor J. Burns Amberson, College of Physicians and Surgeons, Columbia University, New York; Doctor Joseph Aronson, Henry Phipps Institute, Philadelphia; Doctor Howard Bosworth, Barlow Sanatorium, Los Angeles; Doctor Charles Doan, College of Medicine, Ohio State University, Columbus, Ohio; Doctor Johannes Holm, State Serum Institute, Copenhagen, Denmark; Doctor Esmond Long, Henry Phipps Institute, Philadelphia; Doctor Jay A. Myers, University of Minnesota, Minneapolis; Doctor David T. Smith, Duke University, Durham, North Carolina;

Doctor Henry Stuart Willis, William H. Maybury Sanatorium, Northville, Michigan; and Doctor I. C. Yuan, National Institute of Health, Nanking, China.

The United States Public Health Service was represented by Doctors Herman E. Hilleboe, Carroll E. Palmer of the Tuberculosis Control Division, and Hilton V. Voldee, Biologics Control Laboratory of the National Institute of Health, Washington, D. C.

The studies of Doctor Aronson and his co-workers, which were presented at the conference, were made possible by a grant from the Medical Research Committee of the National Tuberculosis Association.

This was one of many coöperative research projects in tuberculosis carried on by the United States Public Health Service and the National Tuberculosis Association.

NOTICE

United States Public Health Service
Fellowships in Health Education

Fellowships leading to a Master's Degree in Public Health in the field of Health Education are being offered to any qualified United States citizen between the ages of 22 and 40, according to a statement released today by the United States Public Health Service, Federal Security Agency. Tuition, travel expenses for field training and a stipend of $100 a month will be provided out of funds furnished by the National Foundation for Infantile Paralysis.

Candidates must hold a bachelor's degree from a recognized college or university and must be able to meet the entrance requirements of the accredited school of public health of their choice. In addition to the degree, courses in the biological sciences, sociology, and education may be required. Training in public speaking, journalism, psychology, and work in public health or a related field are considered desirable qualifications.

The year's training, which begins with the 1947 fall term, consists of eight or nine months' academic work including: public health administration, epidemiology, public health and school education, problems in health education, community organization, and information techniques; and three months of supervised field experience in community health education activities.

Application blanks may be obtained by writing the Surgeon General, United States Public Health Service, Washington 25, D. C., and must be filed prior to March 15, 1947.

Veterans are encouraged to apply and will be paid the difference between their subsistence allowance under the G.I. Bill of Rights and the monthly stipend of $100. Employees of local and state health departments are not eligible since Federal grants-in-aid are already available for such training purposes.

NOTICE

United States Public Health Service
Fellowships in Medical Research

Dr. Thomas Parran, Surgeon General of the United States Public Health Service Federal Security Agency, announces that approximately 120 one-year fellowships in medical research are open to men and women who are graduate science students. These fellowships are part of the program of the National Institute of Health, a unit of the Public Health Service.

A war-created void in scientific manpower offers unlimited opportunity to trained personnel in the public health field, Dr. Parran pointed out. He declared it would take five years or longer to make up the shortage of scientists.

The National Cancer Institute, which operates as a division of the National Institute of Health, also has funds to train approximately 30 physicians in the diagnosis and treatment of cancer, the Surgeon General said. Under a federally financed program, doctors wishing to specialize in this field may be appointed as trainees and be assigned to authorized non-federal, non-profit institutions in various parts of the country.

The National Institute of Health offers research fellowships to graduates of accredited colleges who have majored in such subjects as biology, chemistry, dentistry, entomology, medicine, physics, and other scientific fields.

Paying a yearly stipend of $3,000, Senior Research Fellowships are awarded to men and women who hold Ph.D. degrees in one of the specified scientific subjects. Junior Fellows, who receive $2,400 annually, must hold a master's degree in postgraduate study. Fellowships are for one year from the date of award, and may be renewed for a second year.

Applications for fellowships and traineeships should be sent to the Director, National Institute of Health, Bethesda, Maryland.

The Public Health Service also administers fellowships awarded by the State Department to health personnel from other American republics and the Philippine Islands. Between now and the end of 1947, 100 fellowships will be available to qualified residents of the Philippines. From 15 to 20 fellowships are open through June 30, 1947, to professional persons from other American republics. Applications for these fellowships should be sent to the Surgeon General, United States Public Health Service, Washington 25, D. C.

NOTICE

Seventh Pan-American Congress on Tuberculosis

The President, Dr. Ovidio Garcia Rosell, announces that the Seventh Pan-American Congress on Tuberculosis will be held at Lima, Peru, March 17 to 22, 1947. Distinguished representatives will be present from each of the countries in Central and South America, and, undoubtedly, official delegations and individual members from allied organizations in the United States will attend. More detailed information may be obtained from Dr. Ovidio Garcia Rosell, at Camana 962, Lima, Peru.

THE DISPERSAL OF RESPIRATORY PATHOGENS IN RELATION TO THE OCCURRENCE AND CONTROL OF AIR-BORNE INFECTIONS[1, 2]

O. H. ROBERTSON

In speaking of an infectious disease as air-borne, it should be kept in mind that the descriptive term indicates that the disease may be transmitted through the air or perhaps is acquired principally by this route, but it does not exclude other modes of transmission, such as direct contact with the diseased person or indirect contact with contaminated objects. Our rather fragmentary information suggests that there are marked differences between the various infections of the respiratory tract in respect to their transmissability through the air. The pathogenic agents of certain diseases, such as chicken pox, measles, mumps, epidemic influenza, "Q" fever, psittacosis and coccidioidomycosis, appear to have a marked capacity for aerial infection. Evidence concerning other respiratory infections is much less clear. We have no knowledge as to what percentages of colds, diphtheria, streptococcal disease, meningitis, pneumonia and tuberculosis are acquired by breathing in the infectious agents and what percentages occur as a result of other means of inoculation. Such knowledge is of the greatest importance in planning measures for the control of these diseases.

The concentration of large numbers of persons in Army camps during the war afforded an unusual opportunity for the study of some of these problems. My associates and I had the good fortune to serve on the Commission on Air-Borne Infections[3] which operated under the U. S. Army Epidemiological Board, Preventive Medicine Service, Office of the Surgeon General. While the main purpose of this Commission was the development of methods for the control of acute infections of the respiratory tract it became apparent very early that much more knowledge concerning the mechanism of transmission of such diseases would have to be obtained before effective means of control could be devised. Effort was concentrated principally on one infectious agent, namely, the hemolytic streptococcus since it was felt that this microörganism, by virtue of its characteristic colonies on blood agar and its differentiation into a number of distinct serological types, offered unique opportunities for tracing its spread from person to person. Furthermore, the prevalence and seriousness of this disease during both war and peace times constituted another reason for its intensive study.

[1] From the Department of Medicine, University of Chicago, Chicago, Illinois.

[2] Presented before the Medical Section at the 42nd annual meeting of the National Tuberculosis Association, Buffalo, New York, June 12, 1946.

[3] In addition to the author (Director of the Commission) members who participated actively in the investigations carried out from 1942 to 1946 were Dr. Clayton G. Loosli, Dr. Morton Hamburger, Jr. (Field Director), Dr. Theodore T. Puck, Dr. Henry M. Lemon and Mr. Henry Wise. Other consulting members were Dr. Wilson G. Smillie, Dr. C. Phillip Miller, Dr. Joseph Stokes, Jr., and Dr. William F. Wells.

RELATIONSHIP BETWEEN AIR-BORNE HEMOLYTIC STREPTOCOCCI AND STREPTOCOCCAL INFECTION

The work of Cruickshank (1) in England, who found that the types of hemolytic streptococci infecting burns were the same as those present in the air and the throats of certain of the ward patients, laid the foundation for recent developments in this field. While it seemed likely that the same relationships

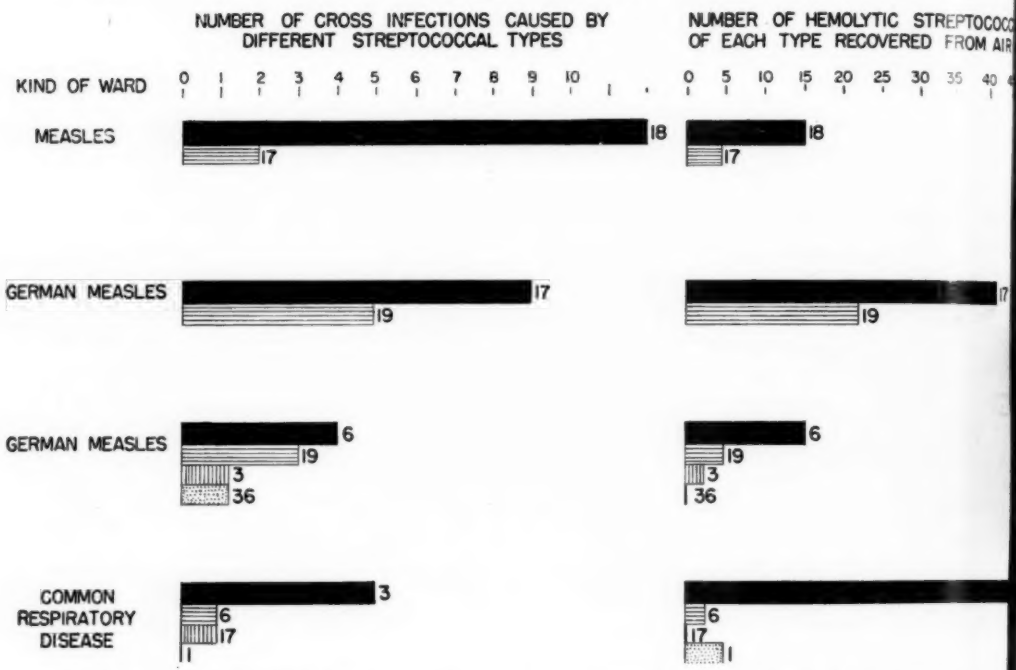

FIG. 1. Relationships between the prevalence of different types of hemolytic streptococci recovered from the air of hospital wards and the incidence of streptococcal infection caused by these types.

The numbers at the right-hand end of the different columns indicate types of streptococci. The several different columns are represented variously in order to distinguish between these streptococcal types.

(Reproduced through the courtesy of Dr. Morton Hamburger, Jr., and the Journal of Infectious Diseases.)

would hold in respect to the spread of hemolytic streptococcal infection of the respiratory tract one could not, in the absence of definite evidence, assume that such was the case. Studies by Hamburger and associates (2) of certain episodes of cross infections with hemolytic streptococci in Army hospital wards housing common respiratory disease provided most informative data on the relationship between air-borne streptococci and cases of streptococcal disease. Cultures of the air[4] in such environments revealed the presence of those streptococcal

[4] Several methods were employed for quantitative bacterial sampling of the air: (*a*) the Moulton sampler (3) which utilized atomization of sterile broth to trap the bacteria in

types causing infection and, furthermore, when such infections were caused by several different types, the predominant air-borne streptococcus was found to be of the same type as that causing the largest number of infections. These relationships are shown in figure 1 taken from Hamburger's paper. Studies in Army barracks showed the same association between the prevalence of certain types of air-borne streptococci and the occurrence of infection due to those types (5).

SOURCES OF AIR-BORNE STREPTOCOCCI

The primary source of respiratory pathogens is, of course, the infected patient or carrier, but studies by certain English and Canadian investigators (6, 7, 8)

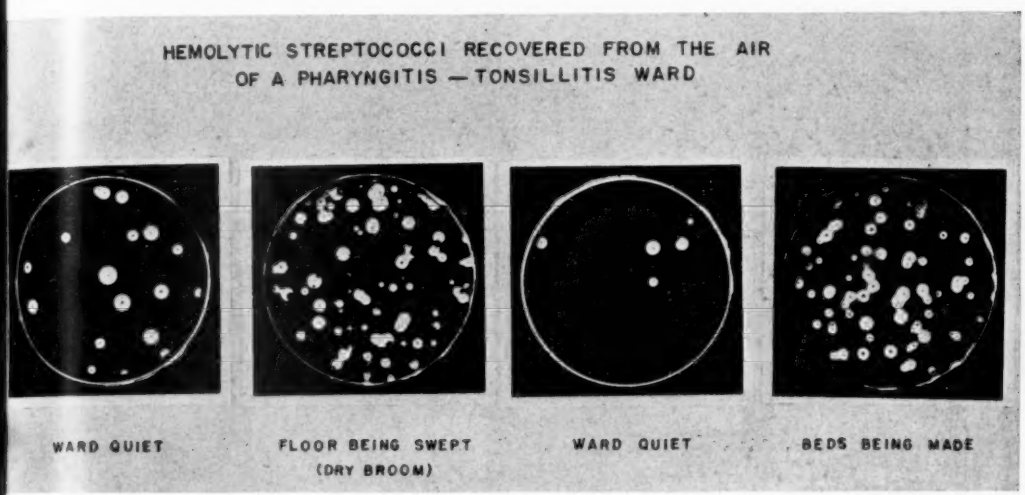

FIG. 2. Photographs of blood agar plates made from bacterial air samples in a ward during varying degrees of activity. The streptococci shown in each plate represent only a small percentage of the total number recovered from the 10 cubic feet of air drawn through the collecting broth.
(Published through the courtesy of Dr. Morton Hamburger, Jr., who collected these data.)

showed that such disease agents as hemolytic streptococci accumulate in bedclothes and floor dust which act as secondary reservoirs from which they are dispersed into the air. Our investigations in wards housing patients suffering from infections due to the hemolytic streptococcus corroborated these earlier findings (5). A direct association was found to exist between ward activities and the relative numbers of hemolytic streptococci recovered from the air. The effects of sweeping the floors and making the beds are shown in figure 2 by photographs of blood agar plates of a series of four air cultures taken in sequence.

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measured quantities of air drawn through the atomizer; (*b*) the bubbler sampler devised by Lemon (4), a relatively simple device which was operated by bubbling air at a very rapid rate through sterile broth; (*c*) blood agar settling plates.

Further studies revealed the fact that it often takes only a few hours to seed the environment heavily with streptococci. This brought importantly to the fore the question as to how the patient contaminates his surroundings. It is usually assumed that coughing, sneezing and talking constitute the principal means of expelling respiratory pathogens. These activities are undoubtedly important in the process and may in certain diseases constitute the chief mechanism of environmental pollution. In streptococcal disease, however, we found another mode by which the infectious material is conveyed from source to external objects, namely, contamination of the hands by blowing the nose and handling the nose and mouth.

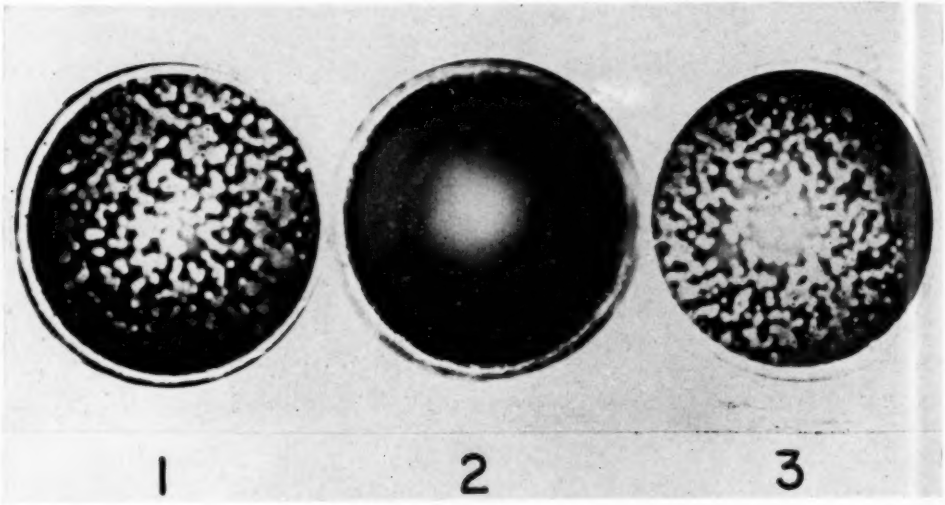

FIG. 3. Photographs of blood agar plates made by inoculating aliquots of nutrient broth in which the nasal carrier washed his hands.

1. Culture before washing.
2. Culture immediately after scrubbing hands thoroughly with soap and water and rinsing in alcohol.
3. Culture after blowing nose.

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STREPTOCOCCAL CONTAMINATION OF ENVIRONMENT BY SALIVA AND NASAL SECRETION

In an investigation of this subject by Hamburger and associates (9) it was observed first that certain patients contaminated their environment to a much greater degree than did others. A search for the principal reservoir of streptococci in the upper respiratory tract of patients with tonsillitis and scarlet fever was centered initially on the saliva and, while it was found that the saliva of such patients frequently contained very large numbers of hemolytic streptococci, the streptococcal content of the individual's saliva could not be correlated constantly with the degree of environmental contamination. It was then discovered

that patients or asymptomatic carriers who harbored hemolytic streptococci in their noses regularly dispersed very much larger numbers of streptococci into their surroundings than did those with these microörganisms present only in the mouth and throat.

Observations on modes of dispersal of streptococci in a large number of nasal carriers showed that blowing the nose caused the extrusion of the greatest number of streptococci (10). Quantitative cultures of handkerchiefs after a single nose blow not infrequently yielded as many as 50 million to 100 million streptococci. Furthermore, marked contamination of the hands occurred during the process. Cultures of a nasal carrier's hands which had been sterilized with alcohol beforehand, yielded thousands to millions of streptococci after the nose blow (figure 3).

Sneezing into a handkerchief held close to the face likewise resulted in the recovery often of large numbers of streptococci but usually not as many as obtained from the nose blow. Coughing on the other hand produced a relatively few small ejection of streptococci.

The nasal carrier not only contaminates his own person and immediate environment but is capable of transmitting streptococci both directly and indirectly to others. In a series of handshaking experiments carried on by Hamburger (11) it was found that nasal carriers transferred to non-carriers hundreds to thousands of hemolytic streptococci through a simple handshake. The highest number recovered from the hand of the recipient immediately after the handshake was 48,000. On the other hand, individuals carrying hemolytic streptococci only in the throat failed to transmit the microörganisms in this manner.

SPREAD OF INFECTION BY NASAL CARRIERS OF HEMOLYTIC STREPTOCOCCI

Additional evidence that the person who disperses large numbers of hemolytic streptococci into his environment constitutes a dangerous carrier was obtained from an epidemiological study of a number of streptococcal infections occurring in hospital wards and barracks (12, 13). With rare exceptions these cases were traced to a nasal carrier of the type streptococcus causing the infections. In certain instances the number of persons infected in rapid succession amounted to a small epidemic. In this same study (12) Hamburger describes an acute hospital epidemic of type I hemolytic streptococcus infection affecting 150 patients which was traced to a cold-food handler. This individual was found to be a nasal carrier of type I hemolytic streptococcus from whose hands were cultured millions of streptococci.

DISPERSAL OF RESPIRATORY PATHOGENS INTO THE AIR BY SNEEZING, COUGHING AND TALKING

Studies on direct contamination of the air by various respiratory activities carried out by a number of workers in this field have shown that sneezing is the most productive of dissemination of bacteria (14, 15, 16, 17). Coughing is less so and talking and laughing result in the ejection of relatively few droplets. The bulk of the material ejected in coughing falls quickly to the nearest surface.

The same is true of the droplets dispersed by talking and laughing. However, the menace of the particular respiratory activity in the transmission of air-borne disease depends on the locus of the pathogenic agent and the frequency of the activity. While the sneeze in hemolytic streptococcus carriers results in the aerial dispersion of large numbers of these microörganisms, the cough produces very few streptococcus-containing droplets (17). This difference can be readily accounted for by the fact that the bulk of the streptococcus-containing saliva is in the front of the mouth where the atomization of the sneeze takes place, while the atomization of the usual cough occurs chiefly in the larynx which probably contains few or no streptococci. In pulmonary infection, on the other hand, it seems most probable that coughing is far more productive of environmental contamination than sneezing quite aside from the relative frequency of the two activities.

SURVIVAL OF RESPIRATORY PATHOGENS IN THE ENVIRONMENT

Studies by the Commission on Air-Borne Infections brought out the finding that the hemolytic streptococcus will survive for relatively long periods of time on contaminated objects (5). Blankets taken from the beds of patients harboring hemolytic streptococci and cultured after four months storage still exhibited considerable numbers of these microörganisms. Furthermore, as one would expect from this finding, the degree of contamination of bed-clothes increases with the time of exposure. While the pneumococcus has been found in viable state in floor dust weeks to a month or more after dispersal from a patient (18) the failure to culture this microörganism from bedding of pneumococcus carriers or patients (19) suggests that its survival outside the body is usually of brief duration. Influenza virus dried on fabrics or glass has been recovered under certain conditions a week or more after the experimental contamination of such objects (20). The length of time this virus will survive outside the body has been found to depend principally on the relative humidity—low humidity favoring long survival (21). By far the hardiest of the common respiratory pathogens is the tubercle bacillus. Its well known capacity for survival outside the body under conditions lethal to other microörganisms points to the secondary reservoirs as having unusual significance in pulmonary tuberculosis.

CONTROL MEASURES

On the basis of the knowledge acquired concerning distribution into the environment of a given respiratory pathogen, namely, the beta hemolytic streptococcus, it has been possible to undertake the investigation of appropriate control measures. Our studies of aerial contamination in Army hospital wards and barracks (5) indicated that the major source of hemolytic streptococci was from floor dust and bed-clothes. Earlier work by English investigators, especially that of Van den Ende, Thomas and associates (6, 7), and more recent observations by ourselves (5, 22) showed that liberation of microörganisms from these secondary reservoirs could be greatly reduced by the application of oils.

Oiling floors: Light paraffin oil applied directly to soft wood floors was found

to be most effective in preventing dispersal of bacteria into the air during sweeping. A single application, to floors previously scrubbed and dried, was found to exert effective dust holding properties for at least six months even in areas where the floors received heavy traffic. Such floors were kept clean by mopping with water only, as soap soon removes the oil. For smooth, non-porous floors, oiled sawdust,[5] an oiled mop or a 10 per cent watery emulsion of the T-13 oil emulsion (23) described below was found to work practically as well. On linoleum or other highly polished floors care must be taken not to apply more than a thin oil layer, otherwise it will become slippery. A compound consisting of urea 5 per cent, Ninol 2 per cent and Roccal 0.1 per cent makes a non-slippery film on the floor which is just as effective as oil and in addition is bactericidal (5). Application to smooth floors must be made daily.

Oiling bedding and other fabrics: A satisfactory oil emulsion devised by Puck and associates (24) for treatment of bed-clothes, consists of a highly purified mineral oil 87 parts and Triton 13 parts. The latter ingredient is a detergent which produces a fine stable emulsion. This treatment is incorporated into the laundry process by means of adding to the third rinse water sufficient T-13 oil emulsion to make a 2 per cent oil-in-water emulsion. Following the regular laundry procedures of extraction and drying, the blankets and other clothes contain approximately 2 per cent of oil by weight and are indistinguishable from regularly laundered clothes except for an added softness and in the case of blankets increased warmth. The process when carried out properly involves no increased fire hazard. Preliminary patch tests with the emulsion had shown no skin reaction and observations by members of the Commission on Air-Borne Infections on the use of such treated bed-clothes, night-clothes and undergarments on thousands of soldiers and hospital patients, including babies, have revealed not a single case of skin irritation attributable to the oiled material. Extensive research by Loosli and coworkers (25) under field conditions has simplified the oiling procedure to a point where any laundry can carry it out easily and inexpensively.

EFFECTS OF OILING BEDDING AND FLOORS

1. *On the bacterial content of the air:* Studies carried on in a large number of Army barracks and Army hospital wards showed that oiling of floors and bedding brought about a reduction in the aerial content of both pathogenic and non-pathogenic bacteria amounting to as much as 90 per cent during periods of greatest activity (5). The number of streptococci and total bacteria cultured from oiled bedclothes was reduced by about the same percentage.[6]

The results of instituting the oiling procedures in a civilian hospital (the Chicago Lying-In Hospital, University of Chicago Clinics) of 180 beds during the

[5] Two gallons of light paraffin oil mixed thoroughly into one hundred pounds of fine drawn sawdust.

[6] Lemon's method of culturing bedding was employed (4). This consisted in substituting a small glass funnel for the air flow meter in the bacterial air-sampling device and using the funnel in the same manner as a vacuum cleaner.

months of February to May, 1946, are shown in figures 4 and 5. During the month of January, previous to oiling, cultures of the air were taken over a period of two hours on two separate days in each of the areas shown in the charts. Each column represents the average of about 8 separate cultures. Beginning in Feb-

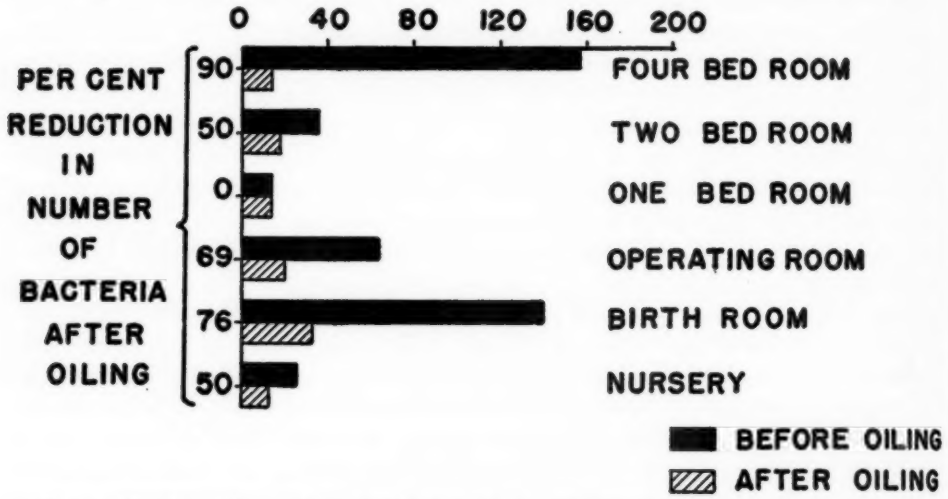

FIG. 4. Number of bacteria per cubic foot of air. Reduction in the bacterial content of the air as a result of application of oil to environment. Air-borne bacteria collected by the bubbler sampler.

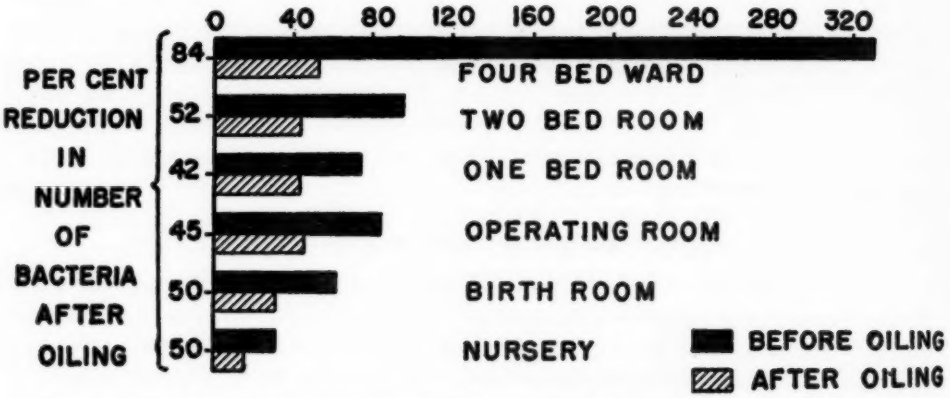

FIG. 5. Number of bacteria per settling plate exposed for one hour. Reduction in the bacterial content of the air as a result of application of oil to environment. Air-borne bacteria collected on blood agar plates.

ruary all articles of every sort coming to the hospital laundry were oil treated with the exception of the personal clothing of internes and nurses. Early in March, three weeks after all the clothing had gone through the laundry at least once, a second series of air cultures were made in the same spaces and under as nearly the same conditions of activity as those of the first cultures.

It will be noted that the percentage reduction of air-borne bacteria brought about by oiling was greatest in the rooms containing 4 patients and least in the single bed rooms.[7] This was shown both by the settling plates which collect the larger bacterial particles and by the broth bubbler sampler which selects the smaller ones. The latter device provides a measure of those bacterial particles which remain suspended in the air for relatively long periods. In the nursery, where the bacterial count was lowest initially, the reduction after oiling was very slight.

During the previous summer a series of bacterial air samples were taken in approximately the same areas as those shown in the two graphs.[8] While the counts were much lower than those secured in January before oiling they were not as low as the counts made during March following the institution of oiling. Thus, even the increased ventilation from open windows was not as effective in reducing aerial contamination as was oiling.

2. *Effect on incidence of acute respiratory disease:* Results of oil treatment of living quarters and hospital wards on the incidence of acute respiratory infections can be considered as yet only preliminary but certain observations suggest a beneficial effect. A study by Wright, Cruickshank and Gunn (26) of the occurrence of streptococcal infection in children's measles wards showed that the incidence of these cross infections in the oiled ward were only one-third of the number occurring in the control, non-oiled ward. Loosli and associates (27, 19), investigating the effect of oiling floors and bedding in a large number of Army barracks, found that the incidence of acute respiratory infections (about half of which were due to the hemolytic streptococcus) in the oiled areas was about 50 per cent of that occurring in the control barracks. On the other hand, oiling does not seem to be as effective in the case of non-bacterial respiratory infections. A joint study by the Commissions on Acute Respiratory Disease and Air-Borne Infections in an Army camp in the South (22) brought out the finding that, while during the period of relatively low incidence of respiratory infection fewer cases occurred in the oiled barracks than in the unoiled, when the respiratory disease season was at its height there was no statistical difference in the number of cases arising in the two areas. The great majority of these infections were of non-bacterial etiology.

AERIAL DISINFECTION

Available evidence suggests that, under some conditions, contamination of the air with respiratory pathogens is due largely or principally to fine droplets expelled by the diseased individual, particularly those patients suffering from certain virus infections of the respiratory tract, for example, the common cold, influenza, chicken pox and others. In such circumstances disinfection of the

[7] No pathogenic bacteria were recovered in this study but it has been the general experience of those working in this field that when pathogens do appear in the air their relative numbers parallel the rise and fall of the total bacterial count.

[8] We are much indebted to Dr. Clayton G. Loosli for planning and supervising this part of the investigation.

air would appear to provide an added and possibly the most important means of controlling the transmission of diseases of this type. Ultraviolet radiation employed in special situations has been shown to be effective in reducing the incidence of certain forms of respiratory infection (28, 29, 30). Disinfection of the air with germicidal vapors, particularly triethylene glycol, offers another possibility in this field. While many data are available on the bactericidal and viricidal properties of triethylene glycol vapor for air-borne respiratory pathogens (31, 32, 33), studies on the utilization of this means of controlling the spread of respiratory diseases are as yet too few to more than indicate promise (34). The extremely minute amounts of triethylene glycol required to produce a highly germicidal atmosphere, combined with the facts that such an atmosphere is indistinguishable from ordinary air, is completely harmless and can be maintained indefinitely, indicate the worthwhileness of further studies on the application of this method to the control of air-borne infections.[9]

IMPLICATIONS FOR THE CONTROL OF TUBERCULOUS INFECTION

Since this meeting is devoted to the subject of tuberculosis it would seem appropriate to inquire how the above described findings may be related to the problem of controlling the spread of tuberculosis by the air-borne route. While it has not been possible, for various reasons, to secure the same detailed information concerning distribution in the environment of tubercle bacilli as has been obtained in the case of the hemolytic streptococcus, sufficient information is available to indicate the direction in which control of certain environments can be most profitably instituted. It has been long known that patients with open pulmonary tuberculosis cause extensive contamination of their surroundings, especially floor dust, bed-clothes and clothing and furthermore, that such tubercle bacilli can be dispersed into the air from these secondary reservoirs in which they may survive for considerable periods of time (35, 36). Recent studies by Duguid (37) have contributed further data on environmental contamination caused by coughing of patients with positive sputa. By exposing glass slides before the mouth of a patient made to cough six times he was enabled to count both the number of droplets ejected and the number of tubercle bacilli in each droplet. Droplets containing tubercle bacilli were ejected by 10 of the 20 patients studied. Individual droplets contained as many as 40,000 bacilli. Of the 410 droplets produced by 120 coughs, 36 were infected. Cultures of the throats of these patients before coughing revealed the presence of tubercle bacilli in the throat secretions of 15 of the 20 patients. Similar cultures of the anterior mouth secretions yielded 10 positive cultures.

Since the bulk of cough droplets are large and fall quickly to the nearest surface and since the principal respiratory activity of the tuberculous patient is coughing, one would expect that the chief source of air-borne tubercle bacilli would be from the secondary reservoirs of bed-clothes and floor dust. Disperal of small infected droplets by sneezing is also quite possible in view of the fact

[9] This present status of the use of triethylene glycol for serial disinfection and the prevention of air-borne infection has been reviewed in a forthcoming paper.

that the tubercle bacilli are present in the mouth secretions as shown by Duguid (37) and others (38). Furthermore, contamination of the hands by infected saliva may well play a rôle in the transmission of tubercle bacilli to the immediate environment and possibly to other individuals. These considerations would indicate the usefulness of oiling procedures for controlling the aerial dispersal of this pathogenic agent particularly in hospitals and sanatoria where bed-clothes and floor dust probably constitute its principal secondary reservoir.

Whether or not disinfection of the air by physical or chemical means could be employed advantageously as an added measure for controlling the transmission of tuberculous infection in human beings cannot be predicted in the absence of pertinent information. It has been shown that air-borne tubercle bacilli are killed by exposure to sufficient ultraviolet radiation and that under certain conditions animals may be protected against air-borne tuberculosis by ultraviolet irradiation (Lurie (39)).

We have not tested the effect of glycols on tubercle bacilli either in the test tube or in the air. Potter (40) has reported that both propylene glycol and triethylene glycol exert a lethal effect on bovine tubercle bacilli *in vitro*. If this observed killing action on tubercle bacilli *in vitro* is of the same nature and degree as that produced by glycols on other respiratory pathogens then one might expect, from the parallelism which we have found between the bactericidal action of glycols *in vitro* and their lethal effect in the air, that under appropriate conditions tubercle bacilli suspended in droplet form in the air would be killed by propylene and triethylene glycol vapors.

DISCUSSION

It is quite obvious from the foregoing presentation that the meagerness of our knowledge concerning air-borne infection makes it very difficult to devise and apply appropriate measures for controlling the various diseases of the respiratory tract. In most cases so little study has been given to the possibility of aerial transmision that information on this subject is virtually nonexistent. While clinical evidence suggests that the infectious agents of a number of the respiratory diseases are carried through the air, their presence in the atmosphere has not been demonstrated, except in a few instances. Even in those few instances little attempt has been made to determine the actual quantity per unit of air. Amother matter of first importance is the mode of dispersal from the infected individual. Whether the pathogenic agent floats in the air as droplet nuclei or is dispersed in larger particles from secondary reservoirs depends on the manner in which the infectious secretion leaves the body. Knowledge as to the time of survival of the infectious agents in the environment under different atmospheric conditions would likewise provide most valuable indications for methods of control.

At the present stage of development of this field, dust suppressive measures would seem to offer the most readily available means of controlling the spread of those diseases whose infectious agents tend to accumulate in the environment. In order to secure the maximum effect from the oiling procedure all washable fabrics

should be treated. In an hospital ward this includes the patients' clothing, pajamas, bathrobes, handkerchiefs, etc. Since dust particles collect on any horizontal surface such areas should be oiled as well as the floor. It should be kept in mind, however, that while properly applied dust control may bring about an adequate reduction of air-borne pathogens in certain situations, other conditions will most likely require aerial disinfection as well to approach the desired result.

Another source of air-borne infection in hospitals has been pointed out first by Willits and Hare (8) and more recently by Bourdillon and Colebrook (41), namely, infected surgical dressings. While much of the danger from removing contaminated dressings can be avoided by using a special room for the purpose, the need for forced ventilation to rid the air of pathogens between dressings is stressed by the latter authors. It would seem possible that the use of oiled dressings on infected wounds might offer an effective means of controlling aerial contamination from this source.

SUMMARY

This communication consists mainly of a summary of certain phases of the work carried out by the Commission on Air-Borne Infections, U. S. Army Epidemiological Board, during the years 1942–1946. The studies were directed principally toward an elucidation of the mode of dispersal and spread of the hemolytic streptococcus which lends itself uniquely to an inquiry of this kind. In support of the rôle played by the air-borne route in the transmission of this disease was the finding of an association between the prevalence of certain types of streptococci in the air and the occurrence of infection due to those types. The number of air-borne hemolytic streptococci was found to depend chiefly on the degree of environmental contamination with this microörganism and the kind and amount of activity within the occupied space. The largest numbers of streptococci were dispersed by persons harboring these microörganisms in their noses and since such persons have been found to be the principal agents in the spread of streptococcal disease they are to be regarded as dangerous carriers. Contamination of his surroundings, bed-clothes, floor and air, by this type of carrier was found to be due principally to blowing the nose, sneezing and handling nose and mouth.

Measures instituted for the control of aerial contamination and the spread of streptococcal infection consisted of oiling floors and bedding to prevent dispersal of the bacteria in the air from these secondary reservoirs and the use of triethylene glycol vapor for disinfection of the air.

The bearing of the results of these studies of streptococcal infections on air-borne transmission of other diseases of the respiratory tract is discussed. The appropriate means of control depend chiefly on the manner in which the particular infectious agent is dispersed into the environment and its length of survival outside the body. Especial consideration in this connection is given to pulmonary tuberculosis.

SUMARIO

Esta comunicación consiste principalmente en un sumario de ciertas fases de la labor llevada a cabo por la Comisión de Infecciones Aerógenas del Consejo Epidemiológico del Ejército de E. U. A., durante los años 1942–1946. Los estudios se encaminaron principalmente a dilucidar la forma de dispersión y propagación del estreptococo hemolítico que es el que se presta más que ningún otro a un estudio de este género. Apoyó el papel desempeñado por la vía aerógena en la transmisión de dicho estado el hallazgo de asociación entre la ocurrencia de ciertos tipos de estreptococos en el aire y la aparición de infección debida a esos tipos. El número de estreptococos hemolíticos aerógenos dependió principalmente de la intensidad de la contaminación del medio ambiente por dicho microbio y de la clase e intensidad de la actividad en el espacio ocupado. Las mayores cantidades de estreptococos fueron esparcidas por personas que alojaban esos microbios en la nariz y como las mismas han resultado ser los principales elementos en la propagación de las estreptococias, debe considerárselas como portadores peligrosos. La contaminación del medio ambiente, la ropa de cama, el piso y el aire por los portadores de ese género resultó deberse principalmente a sonarse, estornudar y manipular la nariz y la boca.

Las providencias utilizadas para combatir la contaminación aérea y la propagación de las estreptococias consistieron en el aceitado de los pisos y la ropa de cama a fin de impedir la dispersión de las bacterias en el aire desde esos reservorios secundarios y en el empleo de vapores de trietileno-glicol para desinfectar el aire.

Discútese la relación del resultado de estos estudios de las estreptococias con la trasmisión aérea de otras enfermedades del aparato respiratorio. El medio apropiado de lucha depende principalmente de la forma en que se dispersa en el ambiente el agente infeccioso dado y la duración de su sobrevivencia fuera del cuerpo. En este sentido se ha concedido atención particular a la tuberculosis pulmonar.

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EXPERIMENTAL AIR-BORNE TUBERCULOSIS AND ITS CONTROL[1,2,3]

MAX B. LURIE

In our studies on the nature of native and acquired resistance to tuberculosis we have used air-borne contagion as a tool of analysis. Following are the highlights of some of the results obtained.

THE ROUTE OF INFECTION IN NATURALLY ACQUIRED TUBERCULOSIS OF THE GUINEA PIG

In tuberculosis of guinea pigs acquired by contact with tuberculous animals under conditions permitting the entrance of tubercle bacilli both by way of the alimentary and respiratory tracts (1), the type of lesion produced depends on the relative intensity of exposure to infection by one or the other channel. With the gradual increase in the intensity of exposure to alimentary infection the disease becomes more and more completely enteric in origin. With the gradual elimination of exposure to alimentary infection tuberculosis is more and more completely engrafted through the respiratory route. In the first instance the mesenteric and cervical nodes are markedly involved and the tracheobronchial nodes are spared. In the latter case the tracheobronchial nodes are massively affected and the mesenteric and cervical nodes are free from the disease. As is well known, tuberculosis characteristically leaves the traces of its progression in the body by the involvement of the nodes draining the portal of entry.

Air-borne contagion of tuberculosis in an animal room: If normal guinea pigs or rabbits are placed in individual cages in a room housing tuberculous animals (2) the exposed individuals acquire a tuberculosis which originates deep in the lung parenchyma and is accompanied by massive tuberculous involvement of the tracheobronchial nodes draining the pulmonary portal of entry. The mesenteric or cervical nodes are not affected. It is clear, therefore, that the disease acquired by these animals is of respiratory origin. Whether the exposed individuals were situated in immediate proximity to tuberculous room-mates or at a considerable distance from them, the incidence of tuberculosis was the same. The infectious agent was, apparently, uniformly distributed throughout the room. Since the disease originated deep in the lung parenchyma through the inspired air, it is evident that the contagion was air-borne.

METHOD OF STUDYING AIR-BORNE CONTAGION OF TUBERCULOSIS IN INBRED RABBITS OF VARYING RESISTANCE TO THE DISEASE

A large manifold is separated in the middle by a fine wire mesh screen (3). On one side of the screen there is a run for artificially infected rabbits which shed

[1] From the Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania.

[2] Aided by a grant from the Commonwealth Fund.

[3] Presented before the Medical Section at the 42nd annual meeting of the National Tuberculosis Association, Buffalo, New York, June 12, 1946.

tubercle bacilli in their urine on a floor bedded with peat moss or other absorbent. On the other side of the screen, in individual cages with open wire mesh work in back and in front, are placed members of highly inbred rabbit families. By means of tuberculin tests and roentgen rays the onset of tuberculosis is determined. The disease thus acquired is of respiratory origin and begins as a single primary focus deep in the lung parenchyma which is always associated, in animals of low genetic resistance, with a massive tuberculous involvement of the draining tracheobronchial nodes and extensive hematogenous generalization. In the resistant animals, the disease tends to remain localized to the portal of entry without involvement of the draining nodes and little hematogenous generalization. The disease acquired by these animals closely corresponds to the different types of tuberculosis seen in man.

Resistance to attack by air-borne tubercle bacilli and resistance to the progress of the ensuing disease: One inbred family has little resistance to attack by tuberculosis (4) as indicated by the short interval between the beginning of exposure and the acquisition of a positive tuberculin reaction. Yet it succumbs to a slowly progressive, localized disease which is of considerable duration, indicating significant resistance to the progression of the naturally acquired disease.

Another inbred family has considerable resistance against attack by natural air-borne contagion of tuberculosis, as shown by the long interval elapsing between the beginning of exposure and the onset of a positive tuberculin reaction, but the acquired disease is rapidly progressive, disseminating in type and of short duration, indicating little resistance to the progression of the naturally acquired infection. Resistance to attack by air-borne contagion of tuberculosis is, therefore, distinct from resistance to the progression of the engrafted disease.

The effect of increasing concentrations of air-borne tubercle bacilli on rabbits of high and low genetic resistance to the disease: If rabbits of high and low genetic resistance to the disease are simultaneously exposed in different experiments to increasing concentrations of tubercle bacilli (4), the effect of this increment is different on animals of high and low resistance. The concentration of air-borne tubercle bacilli is varied by infecting the animals used as sources of contagion by different routes. Intravenous inoculation yields fewer rabbits which shed tubercle bacilli in their urine than when rabbits are inoculated directly into the kidney substance. The concentration of the infectious agent can also be reduced by using peanut shells instead of peat moss as bedding for the sources of contagion. The former do not absorb the tubercle bacilli-laden urine as well as the latter, and hence reduce the number of tubercle bacilli-laden particles thrown up in the air by the sources of contagion. The concentration of tubercle bacilli in the air can be also reduced by introducing ultraviolet lamps in the room, as will be shown later.

It was found that increasing concentrations of tubercle bacilli in the environment of the rabbits of high genetic resistance to the disease increase the incidence of infection, accelerate the rapidity of attack and affect the essential character of the disease in proportion to the concentration of the infectious agent.

In the rabbits of low genetic resistance to the disease, up to a certain level, increasing concentrations of the infectious agent also increase the incidence of the disease and accelerate its onset. The character of the tuberculosis, however, is not affected. It remains rapidly progressive and disseminating in type. Beyond this concentration further increment of the air-borne contagion has no effect on the incidence of the disease, the rapidity of attack or the character of the ensuing disease.

Apparatus for the study of natural quantitative air-borne tuberculosis: A fine suspension of tubercle bacilli, free from clumps, is sprayed with compressed air through a specially designed nozzle (5). The large particles settle out quickly. The invisible droplet nuclei are sucked into a pipe 16 feet long, through a chamber in which rabbits are exposed, by the draft action of a hot flame at the bottom of a chimney devised by Wells. The infected air, after its incineration in the hot flame, is drawn to the outside by a fan. The concentration of the tubercle bacilli in the air breathed by the rabbits is determined culturally by a modified Wells air centrifuge. Since the volume of air breathed by the rabbits in a given time can be determined, and since the number of bacilli present in a unit volume of air is known, the number of bacilli to which the rabbits had been exposed is also given.

It was found that the number of primary tubercles which develop in the lung after three to four weeks (6) is proportional to the number of bacilli in the air inhaled by the rabbits. These tubercles correspond to the primary lesions seen in man. However, there is great variation between individual rabbits inhaling the same infected air, both as to the number of tubercles developed and their progression. When rabbits of known genetic resistance are exposed to small numbers of droplet nuclei (3) the rabbits of high resistance develop a slowly progressive disease which is limited to the portal of entry, the lung, without dissemination by hematogenous or lymphogenous routes. In its essentials, the disease corresponds to that seen in adults and described as localized ulcerative pulmonary phthisis. The rabbits of low genetic resistance exposed simultaneously to the same number of tubercle bacilli develop a rapidly progressive disease with marked lymphogenous and hematogenous dissemination.

THE PREVENTION OF NATURAL AIR-BORNE CONTAGION OF TUBERCULOSIS IN RABBITS

If the droplet nuclei introduced into the exposure chamber are exposed to ultraviolet radiation (5), all but a few bacilli are killed after a few seconds' exposure. It would follow therefore that, if natural air-borne contagion is caused by droplet nuclei, that tuberculosis thus acquired should be prevented by suitable ultraviolet irradiation of the air.

Accordingly the following experiment was set up (7). The room housing the manifold described above is divided by a solid partition extending from the floor to the ceiling, which also divides the interior of the manifold into two equal, air-tight halves. One room is not irradiated. The other room is irradiated. Ultraviolet lamps are placed horizontally in the space between the infected and exposed animals in each of the three tiers. In addition, the air of the experimen-

tal room as a whole is irradiated by ultraviolet lamps placed above and below this section of the manifold. Litter mates of the highly inbred families of high and low resistance are placed in corresponding positions in the contact cages of both rooms. The infected rabbits serving as sources of contagion are interchanged daily between the two rooms. Thus both the host and parasite variables are equalized.

At the end of a year, 11 of the 15 contacts in the unirradiated room died of tuberculosis. These included rabbits of high and low resistance to the disease. None of the 15 litter mates of the same genetic resistance, exposed for the same time, to the same contagion in the irradiated rooms developed tuberculosis. Three additional rabbits in the control room developed tuberculin sensitivity without any tuberculous changes at autopsy. None of the protected rabbits developed tuberculin sensitivity. Only one rabbit in the irradiated room developed a regressive microscopic tubercle. Thus a 73 per cent mortality from tuberculosis was eliminated by ultraviolet radiation. It is clear that the intensity of contagion obtaining in this experiment is much greater than is likely to occur in human life. It is probable, therefore, that untraviolet radiation may control air-borne contagion of human tuberculosis.

SUMMARY

Methods of studying both natural and quantitative air-borne contagion of tuberculosis in rabbits and guinea pigs are described. The effect of the number of respired tubercle bacilli on rabbits of high and low genetic resistance to the disease is outlined. Resistance to attack by natural air-borne contagion is distinguished from the resistance to the progress of the engrafted disease.

Ultraviolet light kills tubercle bacilli suspended in the air. Experiments are described whereby suitable ultraviolet irradiation of the air completely protected rabbits from an air-borne contagion of tuberculosis of such intensity which killed 73 per cent of rabbits of the same genetic constitution, exposed to the same contagion within the same period of one year.

SUMARIO

La luz ultravioleta destruye los bacilos tuberculosos suspendidos en el aire. Los experimentos descritos muestran que la apropiada irradiación ultravioleta del aire protegió absolutamente a los conejos contra una infección tuberculosa aérea de tal intensidad que mató a 73 por ciento de los conejos de la misma constitución genética, expuestos a la misma infección durante el mismo período de un año.

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DISCREPANCIES BETWEEN CLINICAL-RADIOLOGICAL AND BRONCHOSPIROMETRIC FINDINGS[1]

RAÚL F. VACCAREZZA, ALFREDO LANARI AND ALBERTO SOUBRIÉ

The separate examination of each lung, which at one time was the most sought after achievement in the study of the functional capacity of the respiratory system, is now a well established practice. The usefulness of this method in solving certain problems of respiratory physiopathology was demonstrated by Jacobaeus and coworkers, who were the first to establish: (*a*) the normal functional value of each lung (1); (*b*) the percentage of blood circulation in each lung under normal and pathological conditions (2); (*c*) the influence of postural changes (2); (*d*) the possibility of one lung compensating for the lost function of the other (3); and (*e*) the changes in ventilation produced by the impaired output of carbon dioxide (4).

Further studies in this field have been carried out at the Department of Tuberculosis of the Faculty of Medicine of Buenos Aires, with the following results: the identity between alveolar and residual air has been established (5); atelectasis has been produced by the aspiration of residual air (6); the alveolar air of each lung has been studied in normal and pathological cases (7); the volume of ventilation and of oxygen consumption of each lung has been determined and correlated with postural changes (8), and the cardio-pulmonary movements have been studied in each lung (9).

Several papers have been published in the United States dealing with the valuable clinical data obtainable from bronchospirometric examinations (10, 11, 12). Whitehead and his associates (13), as well as Wright and Woodruff (14), have confirmed the earlier work of Jacobaeus, concerning the circulation of each lung and the possibility of the function of one lung being taken over by the other.

In this paper, which is of a purely clinical nature, we wish to stress certain unexpected results obtained in our study of the functional capacity of separate lungs. The cases mentioned have been chosen from over 420 bronchospirometric examinations performed between 1939 and 1945.

In all these cases intubation was performed with Gebauer's, and occasionally with Zavod's, catheter (15). It is reassuring to note that, in the five years that have elapsed since we began doing these intubations, only two accidents have occurred both due to pantocain intolerance, and they were not of a serious nature.

In an insignificant number of cases a transitory increase was noted in such symptoms as cough and expectoration. Intubation was not performed in patients with obvious laryngeal lesions, in those in whom the pulmonary lesions were deemed to be very active, or in patients who had suffered a recent hemop-

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tysis. Great care was taken in the examination of patients with asthma, because asthmatic attacks may easily be precipitated by intubation.

Brief summaries are presented of 15 patients in whom the bronchospirometric findings are in disagreement with the clinical and radiological impressions as to the functional capacity of each lung.

A brief comment follows each case report in which an attempt is made to explain the reason for these apparently paradoxical findings, and in which the clinical implications are stressed.

CASE REPORTS

Case 1: E. P., female, age 25. Register No. 201. Extensive fibrocaseous pulmonary tuberculosis, with excavation of the left lung.

Roentgenological findings (29/5/44): Costodiaphragmatic and mediastinal pachypleuritis. Right lung: a few small conglomerated nodular lesions near the base. Left lung: disseminated nodules, large and small, especially in the upper and middle zones, with an infraclavicular cavity (figure 1).

Spirometry (14/6/44): Breathing reserve[2] reduced (61 per cent). Oxygen saturation of arterial blood satisfactory during moderate exertion.

Bronchospirometry (8/8/44):

	Right Lung	*Left Lung*
Minute volume of ventilation	6,900 cc.	5,800 cc.
Oxygen consumption	145 cc.	113 cc.
Ventilation equivalent	4.7 lt.	5.1 lt.

Summary: Normal functional relationship between the two lungs. Oxygen intake of the right lung is 57 per cent and that of the left lung is 43 per cent.

Comment: The bronchospirometric examination was carried out to find out whether it was feasible to perform surgical collapse of the left lung, because an intrapleural pneumothorax was considered impossible due to the presence of pleural adhesions. The results show that the functional relationship between the two lungs was unaltered, notwithstanding the extensive lesions of the left lung. The thickening of the right basal pleura explains this unexpected finding. The functional value of this lung was a definite contraindication to the proposed operation, because the collapse of the left lung, further reducing the respiratory reserve, would almost certainly have lead to a severe respiratory insufficiency.

Case 2: T. F., male, 28 years old. Register No. 4759. Extensive bilateral fibrocaseous pulmonary tuberculosis, more marked on the left side.

Roentgenological findings (4/12/43): Right lung: costodiaphragmatic sinus obliterated; right mediastino-diaphragmatic triangle outlined by a dense and undulated border; some fibrotic strands extending from the hilum to the apex. Left lung: extensive shadow in the mid-zone, of a nodular, exudative nature, with a tendency to coalesce. Heart slightly deviated to the right. (Figure 2.)

Spirometry (22/12/43): Good breathing reserve (87 per cent). There appears to be a slight degree of arterial unsaturation.

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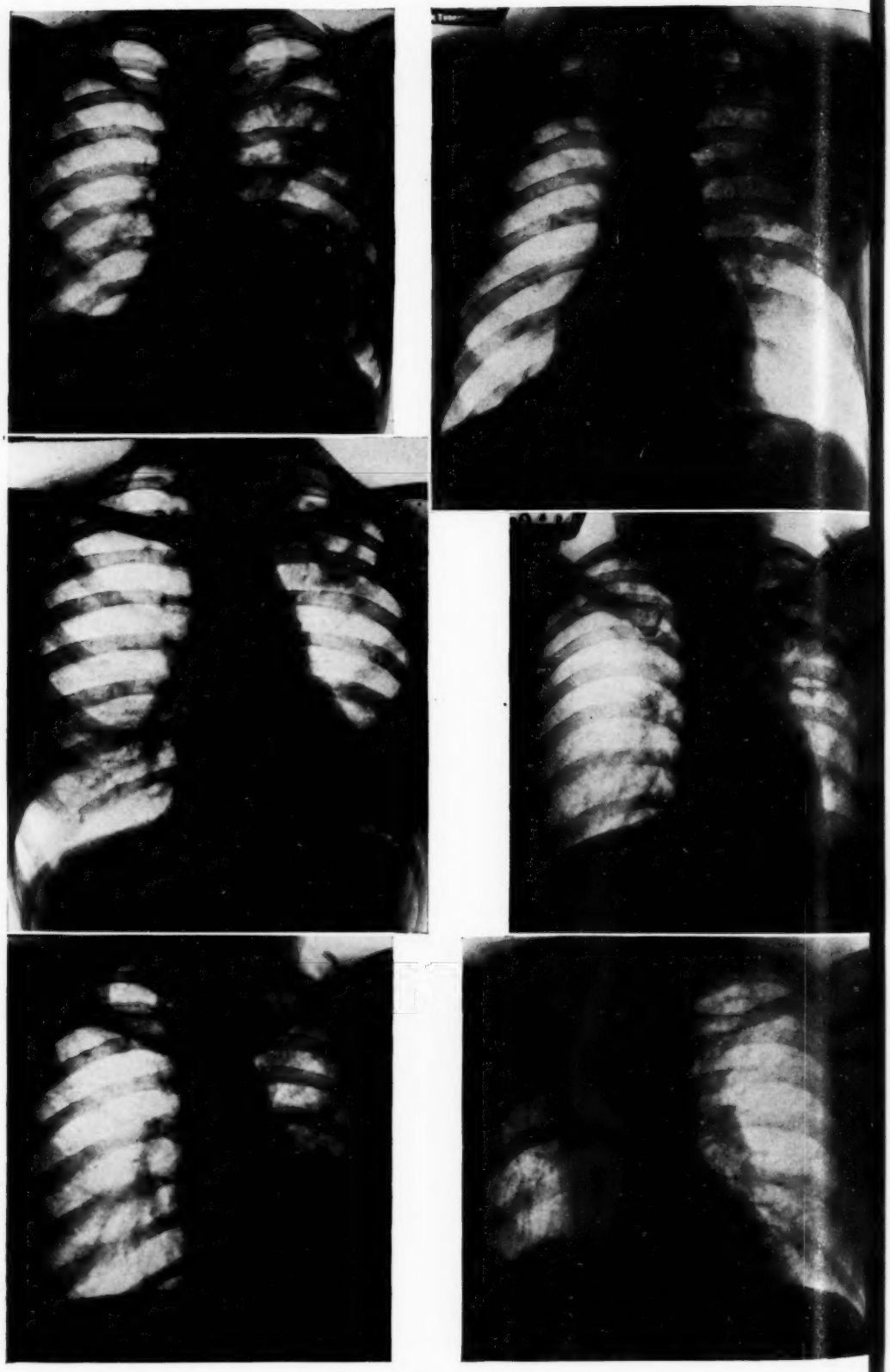
[2] "Breathing reserve" is used as defined by Cournand and Richards (Am. Rev. Tuberc., 1941, *44*, 26).



FIGS. 1–6

FIG. 1. upper left; FIG. 2. upper right; FIG. 3. centre left; FIG. 4. centre right; FIG. 5. lower left; FIG. 6. lower right. (See case reports.)

Bronchospirometry (16/12/43):

	Right Lung	*Left Lung*
Vital capacity	1,223 cc.	1,368 cc.
Complementary air	269 cc.	393 cc.
Supplementary air	601 cc.	642 cc.
Minute volume of ventilation	5,200 cc.	5,000 cc.
Oxygen consumption	124 cc.	228 cc.
Ventilation equivalent	4.2 lt.	2.1 lt.

Summary: 65 per cent of the oxygen intake is through the left lung.

Comment: The decreased functional value of the right lung is explained by the basal pleuritis and by the probable retraction of the lower lobe, with a compensatory distension of the other two lobes. It is interesting to note that the pachypleuritis and emphysema of this lung decrease the oxygen consumption more than the ventilation. The left lung fully compensates this functional decrease in spite of its rather extensive lesions and of the pleural symphysis, encountered when an attempt was made to produce an artificial pneumothorax.

Case 3: A. C., male, 36 years old. Register No. 4577. Extensive bilateral fibrocaseous pumonary tuberculosis with ulceration in the left lung.

Roentgenological findings (16/12/43): Right lung: disappearance of the costodiaphragmatic sinus with a deformed and flattened diaphragm; hilar shadow increased with dense fibrotic strands radiating towards the apex. Left lung: exudative lesions, confluent in the middle and lower zones, with a cavity measuring 5 cm. in diameter in the mid-zone. Cardiac shadow deformed by pleural retraction. Subsequent fluoroscopic examinations carried out during the following months, before the first bronchospirometry was performed, showed little change in the radiological picture.

Spirometry (31/5/44): Reduced breathing reserve (75 per cent). Normal arterial oxygen saturation.

Bronchospirometry: (First attempt, using Gebauer's catheter, 23/5/44)

	Right Lung	*Left Lung*
Vital capacity	1,243 cc.	1,160 cc.
Complementary air	559 cc.	663 cc.
Supplementary air	165 cc.	165 cc.
Minute volume of ventilation	10,400 cc.	9,600 cc.
Oxygen consumption	62 cc.	414 cc.
Ventilation equivalent	16.7 lt.	2.3 lt.

Summary: The right lung accounts for only 13 per cent of the total oxygen intake. This surprising result induced us to repeat the examination.

(Second attempt, using Zavod's catheter, 10/8/44)

	Right Lung	*Left Lung*
Vital capacity	891 cc.	1,036 cc.
Complementary air	331 cc	331 cc.
Supplementary air	124 cc.	145 cc.
Minute volume of ventilation	9,200 cc.	10,800 cc.
Oxygen consumption	145 cc.	228 cc.
Ventilation equivalent	6.3 lt.	4.7 lt.

Summary: The right lung still shows poorer function. It only accounts for 38 per cent of the total oxygen intake. The relative improvement in function as compared to the first examination is due to the extension of the lesion in the left lung.

Comment: The functional impairment of the right lung can be attributed to the pleural lesions and to the diffuse fibrotic emphysema, remains of a five-year-old tuberculous lesion in that lung.

This patient died on October 25, 1944, after a profuse hemoptysis. Autopsy showed a marked fibrosis of the upper and lower lobes of the right lung, with distention of the middle lobe. The roentgenogram did not reveal any sign of this extreme lobar retraction. The clinico-radiological findings induced us to believe that the right lung had a better oxygen consumption than the left. Its actual slight functional participation, revealed by bronchospirometry, is explained by the fact that only the considerably distended middle lobe was functioning. The left lung compensated for this impairment of the right lung in spite of its extensive lesions and of the pleural symphysis. That the degree of compensation was gradually diminishing was shown by the second bronchospirometry.

Case 4: N. P., female, 22 years old. Bilateral fibrocaseous pulmonary tuberculosis, more marked and excavated on the left side.

Roentgenological findings (22/12/44): Right lung: vascular markings slightly increased; disseminated large and small nodules in the lower lung field; partially obliterated costodiaphragmatic sinus. Left lung: retroclavicular cavity with dense and thickened walls; scattered large and small nodules in the rest of the lung. Upper mediastinum deviated towards the left. (Figure 3.)

Spirometry (23/12/44): Much reduced breathing reserve. Arterial unsaturation appears with moderate exertion.

Bronchospirometry (21/12/44):

	Right Lung	*Left Lung*
Vital capacity	974 cc.	82 cc.
Complementary air	165 cc.	20 cc.
Supplementary air	538 cc.	20 cc.
Minute volume of ventilation	9,400 cc.	2,200 cc.
Oxygen consumption	352 cc.	20 cc.
Ventilation equivalent	2.6 lt.	11 lt.

Summary: Only 5 per cent of the oxygen consumption is accomplished by the left lung.

Comment: It is obvious that, judging from the radiological examination, we would expect that the functional participation of the left lung was greater than it really was. The discrepancies in this case are probably due to the pleural thickening and to the presence of bronchial lesions with what we term "air filtration," in addition to the existing pulmonary lesions. The auscultation of the chest, performed both with the catheter in place and without the catheter, revealed a marked decrease in the breath sounds over the left hemithorax with loud rhonchi audible over the back. No respiratory sounds could be heard in front. Bronchoscopy was not carried out because of frequent hemoptysis.

Case 5: E. N., female, 31 years old. Register No. 23469. Bilateral fibrocaseous pulmonary tuberculosis, predominating on the left side.

Roentgenological findings (22/2/45): Right lung: disseminated small nodules, especially in the apex. Left lung: retraction of upper ribs; large cavity in the apex below which a second cavity is seen containing a fluid level; elevation of the left diaphragm; mediastinum deviated to the left. (Figure 4.)

Bronchoscopy (18/4/45): Left main bronchus reduced in its main diameter; the angle formed with the trachea is rather sharp owing to fibrotic retraction, which renders a correct examination of the whole surface of this bronchial tube almost impossible.

Spirometry (11/10/44): Reduced breathing reserve (71 per cent).

Bronchospirometry (20/2/45):

	Right Lung	*Left Lung*
Vital capacity	974 cc.	41 cc.
Complementary air	207 cc.	—
Supplementary air	538 cc.	—
Minute volume of ventilation	8,080 cc.	1,000 cc.
Oxygen consumption	310 cc.	41 cc.
Ventilation equivalent	2.6 lt.	2.4 lt.

Summary: The left lung is practically excluded from a functional point of view.

Comment: The roentgenogram reveals a surprisingly well aerated appearance of the left lung, compared to its functional value which is practically non-existent. Auscultation, which was performed with the catheter in place and the balloon inflated, and also without the catheter, revealed loud bronchial breathing. We are dealing with a case of "bronchial air filtration."

Case 6: N. D., female, 22 years old. Register No. 18917. Fibrocaseous pulmonary tuberculosis, bilateral, but predominantly left-sided. Left artificial pneumothorax was performed in 1942 and discontinued after two months on account of the development of pleural symphysis.

Roentgenological findings: Right lung: increase of pulmonary markings with some scattered small nodules, especially in the upper and middle zones. Left lung: costal retraction; elevated diaphragm; calcifications in the apex; apical and marginal pleural thickening. Mediastinum deviated to the left. (Figure 5.)

Bronchoscopy (27/11/43): Generalized congestion of the trachea and left main bronchus; (7/10/44) congestion of trachea and bronchial tubes; retention of secretions in the left main bronchus.

Spirometry (29/9/44): Decreased breathing reserve (72 per cent). Slight arterial unsaturation with moderate exertion.

Bronchospirometry:

	Right Lung	*Left Lung*
Vital capacity	974 cc.	0
Complementary air	207 cc.	0
Supplementary air	391 cc.	0
Minute volume of ventilation	11,200 cc.	0
Oxygen consumption	269 cc.	0
Ventilation equivalent	4.1 lt.	—

Summary: The left lung is functionally non-existent. The clinico-radiological examination led one to believe that there was a marked impairment of its functional capacity, but not that this had completely disappeared.

Comment: An irreversible type of collapse therapy was possible on the left side, notwithstanding the deficient total function, since the gaseous interchange was entirely dependent on the right lung. The functional absence of the left lung proves that there must have been a bronchial stenosis with "air filtration" in addition to the parenchymatous and pleural lesions demonstrated radiographically.

Case 7: O. C., male, 43 years old. Register No. 23140. Bilateral fibrocaseous pulmonary tuberculosis with excavation on the right side.

Roentgenological findings (19/5/44): Right lung: large cavity with thickened walls, apparently insuflated, occupying the apex; marked pleural lesions. Left lung: increased pulmonary markings and fibrous lesions in the region of the apex. Mediastinum deviated to the right. (Figure 6.)

Bronchospirometry (10/8/44):

	Right Lung	*Left Lung*
Vital capacity	62 cc.	704 cc.
Complementary air		145 cc.
Supplementary air		186 cc.
Minute volume of ventilation	1,800 cc.	10,200 cc.
Oxygen consumption		393 cc.
Ventilation equivalent		2.6 lt.

Summary: The right lung is practically useless from the functional point of view. It does not participate in oxygen consumption.

Comment: Bronchospirometry was performed prior to a right thoracoplasty. The non-existence of the right lung from the functional point of view supports the surgical treatment, in spite of the low ventilatory reserve evidenced by the total examination. Perhaps a bronchial stenosis in addition to the marked pleural and pulmonary lesions would offer an explanation for the contrast between the radiological and the bronchospirometric findings.

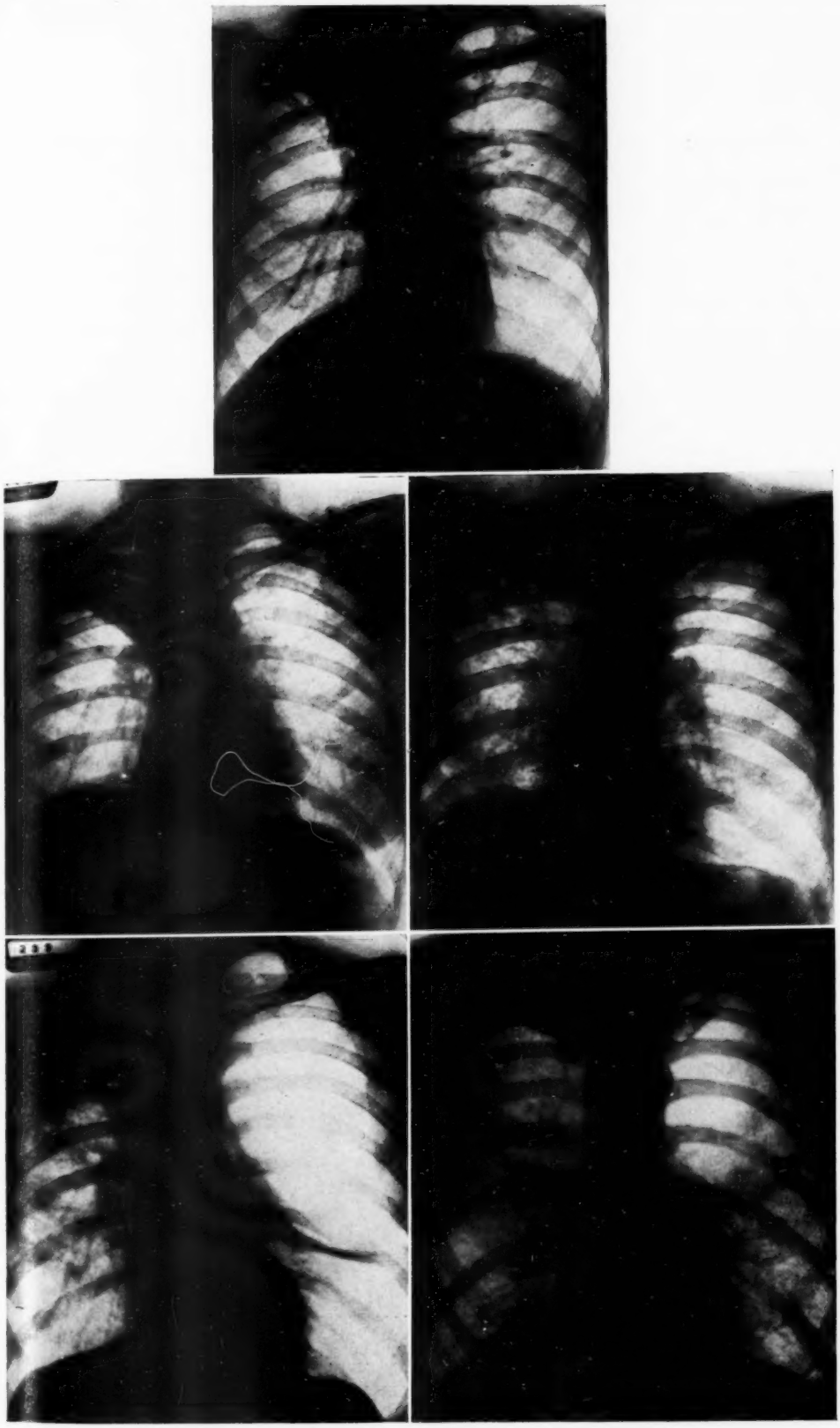
Case 8: A. L., female, 29 years old. Register No. 13335. Extensive fibrocaseous pulmonary tuberculosis, bilateral, more marked on the left side, with a large cavity in the left lung.

Roentgenological findings (2/3/42): Scattered small and large nodules in the right lung. Left lung: large cavity with a fluid level in the upper third of the lung; the remaining lung fields have a veiled appearance.

Spirometry (8/10/41): Much reduced breathing reserve.

Bronchospirometry (7/4/42):

	Right Lung	*Left Lung*
Vital capacity	787 cc.	456 cc.
Complementary air	269 cc.	82 cc.
Supplementary air	248 cc.	124 cc.
Minute volume of ventilation	7,800 cc.	4,100 cc.
Oxygen consumption	352 cc.	20 cc.
Ventilation equivalent	2.2 lt.	25.0 lt.



FIGS. 7–11

FIG. 7. upper; FIG. 8. centre left; FIG. 9. centre right; FIG. 10. lower left; FIG. 11. lower right. (See case reports.)

Summary: Only 6 per cent of the oxygen intake takes place through the left lung.

Comment: The extremely poor ventilation equivalent of the left lung (25 litres) shows that the large cavity has a wide communication with the bronchial tree. This lung, which contributes only 6 per cent to the total oxygen intake, has no functional value. This finding would favor the possibility of an extensive thoracoplasty of the left side, in spite of the small breathing reserve as revealed by the spirometric examination, which in all probability will remain unaltered after operation.

Case 9: V. H., male, 37 years old. Register No. 15957. Bilateral fibrocaseous pulmonary tuberculosis, predominating on the right side. Right upper lobe retracted and ulcerated. Right pneumothorax unsuccessfully attempted. Right phrenicectomy was performed in 1935.

Roentgenological findings (6/6/42): Right lung: Numerous small cavities in upper lobe, which appears markedly retracted. Lung parenchyma has an emphysematous appearance in the mid-zone; lower zone normal. Left lung: increased hilar shadow, with emphysema of the upper and lower zones. (Figure 7.)

Spirometry (1/7/42): Reduced breathing reserve.

Bronchospirometry (21/8/42):

	Right Lung	*Left Lung*
Vital capacity	663 cc.	207 cc.
Complementary air	145 cc.	41 cc.
Supplementary air	228 cc.	41 cc.
Minute volume of ventilation	8,900 cc.	4,600 cc.
Oxygen consumption	228 cc.	82 cc.
Ventilation equivalent	3.9 lt.	5.6 lt.

Summary: The left lung accounts for 25 per cent of the total oxygen consumption.

Comment: In this case the left lung which radiologically appears to be the least affected, accounts for only one-fourth of the total oxygen consumption. This is best explained by the presence of fibrosis and emphysema. The poor ventilation equivalent confirms this interpretation. The results in this case are most surprising, especially in view of the compensatory distention which has taken place in the right lung, At present the right diaphragm functions normally. Surgical collapse of the right lung was contraindicated by the poor respiratory reserve.

Case 10: A. Z., female, 37 years old. (Private patient.) Bilateral fibrocaseous pulmonary tuberculosis, more advanced in the right lung. Ulcerated lesion in the right lung.

Roentgenological findings: Right lung: medium-sized retroclavicular cavity. Left lung: pachypleuritis. A few scattered small nodules in mid-zone.

Spirometry (2/5/45): The breathing reserve is normal if related to the patient's weight. However, a slight degree of arterial unsaturation appears with moderate exertion.

Bronchospirometry (3/5/45):

	Right Lung	*Left Lung*
Vital capacity	1,451 cc.	808 cc.
Complementary air	228 cc.	248 cc.
Supplementary air	849 cc.	393 cc.
Minute volume of ventilation	7,200 cc.	3,800 cc.
Oxygen consumption	248 cc.	145 cc.
Ventilation equivalent	2.9 lt.	2.6 lt.

Summary: The right lung accounts for 62 per cent of the total oxygen consumption.

Comment: The diminished functional value of the left lung, which roentgenologically appears to be less involved, is most likely due to the fact that an artificial pneumothorax was performed in 1937, because of extensive ulcerated lesions in the mid-zone. This pneumothorax was abandoned after eighteen months due to a progressive pleural symphysis. It is our opinion that the decreased oxygen consumption of the left lung is caused by the healed pulmonary and pleural lesions. If any surgery is attempted on the right lung, it must be performed with the greatest care.

Case 11: G. P., female, 32 years old. Register No. 23316. Bilateral fibrocaseous pulmonary tuberculosis, ulcerated and predominating in the right side. A fruitless attempt was made to perform an artificial pneumothorax on this side.

Roentgenological findings (4/11/44): Right lung: retraction of the upper ribs and displaced upper mediastinum; upper lobe retracted, with a large cavity; scattered small nodules in the remainder of the lung. Left lung: small excavated infraclavicular infiltration. (Figure 8.)

Spirometry (23/11/44): Small breathing reserve (60 per cent).

Bronchospirometry (25/11/44):

	Right Lung	*Left Lung*
Vital capacity	663 cc.	891 cc.
Complementary air	310 cc.	414 cc.
Supplementary air	145 cc.	228 cc.
Minute volume of ventilation	4,500 cc.	5,600 cc.
Oxygen consumption	155 cc.	165 cc.
Ventilation equivalent	2.9 lt.	3.3 lt.

Summary: The right lung accounts for 45 per cent of the oxygen consumption.

Comment: The surprisingly good functional value of the right lung is due to the lower lobes, which are functionally intact. The presence of a satisfactory ventilation equivalent in spite of the pleural lesions and of the large cavity in the upper lobe, would suggest a partially obstructed bronchial communication.

Case 12: A. R., male, 43 years old. Register No. 22549. Fibrocaseous, predominantly fibrous, pulmonary tuberculosis with excavation of the right lung, which appears to be the most affected. Pneumothorax not possible due to pleural adhesions.

Roentgenological findings (22/4/44): Mediastinum displaced towards the right; elevated diaphragm on the right. Right lung: Medium-sized cavity in the upper zone. Old fibrotic lesions in the remainder of the lung. Left lung: veiled shadow covering the apex. Obliterated costodiaphragmatic sinus. (Figure 9.)

Spirometry (19/7/44): Good breathing reserve (80 per cent).

Bronchospirometry (20/8/44):

	Right Lung	*Left Lung*
Vital capacity	870 cc.	1,596 cc.
Complementary air	62 cc.	396 cc.
Supplementary air	269 cc.	642 cc.
Minute volume of ventilation	11,700 cc.	15,200 cc.
Oxygen consumption	82 cc.	352 cc.
Ventilation equivalent	14.2 lt.	4.3 lt.

Summary: The right lung accounts for 18 per cent of the total oxygen consumption.

Comment: The bronchospirometric examination was performed for the purpose of establishing the possibility of a surgical collapse of the right lung. The slight functional value of this lung and its poor ventilation equivalent are due to the extensive fibrotic lesions. The indices of ventilation (vital capacity and maximum breathing capacity) are misleading in this case.

Case 13: S. G., male, 33 years old. Register No. 13520. Bilateral fibrocaseous pulmonary tuberculosis. Left thoracoplasty.

Roentgenological findings (21/10/41): Right lung: disseminated small nodules in the upper lung field. Left lung: thoracoplasty with resection of the first eight ribs. Aerated parenchyma in the lower lung field.

Spirometry (18/3/42): Slight respiratory insufficiency during exercise. No ventilatory reserve.

Bronchospirometry (20/3/42):

	Right Lung	*Left Lung*
Vital capacity	787 cc.	0
Complementary air	145 cc.	0
Supplementary air	145 cc.	0
Minute volume of ventilation	14,000 cc.	0
Oxygen consumption	331 cc.	0
Ventilation equivalent	4.2 lt.	—

Summary: There is a broncho-parietal fistula on the left side, communicating with the exterior, allowing 250 cc. of air to pass per minute.

Comment: The results of the bronchospirometric examination were really extraordinary. As could be clearly seen in the chart, the curve corresponding to the left lung descends instead of rising, crossing the curve of the right lung. This would indicate that the left spirometer is in communication with the atmospheric air, by means of the broncho-parietal fistula.

Case 14: C. C., male, 24 years old. Right fibrocaseous pulmonary tuberculosis, ulcerated. Left giant gaseous cyst.

Roentgenological findings (10/1/42): Costal retraction; mediastinum deviated towards the right. Right lung: confluent nodular lesions in upper and middle zones with double excavation; some mixed small nodules in the rest of the lung. Left lung:enormous gaseous cyst occupying the upper two thirds of the left lung field. (Figure 10.)

Spirometry (17/2/43): Satisfactory breathing reserve.

Bronchospirometry (8/5/42):

	Right Lung	*Left Lung*
Vital capacity	1,098 cc.	1,036 cc.
Complementary air	248 cc.	269 cc.
Supplementary air	456 cc.	290 cc.
Minute volume of ventilation	5,800 cc.	7,000 cc.
Oxygen consumption	393 cc.	41 cc.
Ventilation equivalent	1.5 lt.	17.0 lt.

Summary: The lung with the cyst accounts for 10 per cent of the oxygen intake and for more than 50 per cent of the ventilation.

Comment: Ample ventilation in the left lung, with reduced oxygen consumption (the ventilation equivalent being 17 litres) which shows that the cyst has a widely patent bronchus. It is noteworthy that the ventilation equivalent of the right lung is satisfactory in spite of the extent of the lesions in this lung.

Case 15: J. E., male, 45 years of age. Register No. 15975. Fibrocaseous pulmonary tuberculosis, preponderantly fibrous. Vesicular emphysema.

Roentgenological findings (29/5/42): Right lung: increased pulmonary markings, especially in the vicinity of the hilum. Left lung: vesicular type of emphysema in the upper two-thirds; the lower lung fields have the same appearance plus some additional fibrotic lesions. (Figure 11.)

Bronchospirometry (30/6/42):

	Right Lung	*Left Lung*
Vital capacity	1,243 cc.	746 cc.
Complementary air	310 cc.	145 cc.
Supplementary air	373 cc.	228 cc.
Minute volume of ventilation	9,200 cc.	7,000 cc.
Oxygen consumption	290 cc.	178 cc.
Ventilation equivalent	3.1 lt.	3.9 lt.

Summary: The right lung accounts for 62 per cent of the oxygen intake.

Comment: The ventilation equivalent of the left lung is not so poor considering the pneumonectasia. This indicates that there is no communication between the cyst and the bronchial tree, as occurred in the previous case. The influence on ventilation of the pneumonectasia is remarkably small.

DISCUSSION

In the majority of cases the separate functional examination of each lung confirms the impressions obtained as to their functional capacity by the routine clinical-radiological examination. However, that this is not so in every case is shown by the cases presented in this paper, in which a marked contrast exists between the anatomical lesions of the lungs and their true functional value. In some instances both the functions of ventilation and of oxygen consumption are concerned, in others only the latter. This functional dissociation, which is of considerable interest from the practical point of view, can only be fully appreciated by means of a bronchospirometric examination. At times both the clinical and radiological findings are in disagreement with the functional results; at others it is only the roentgenogram that is misleading, the physical examination and the fluoroscopic picture being in complete agreement with the bronchospirometric determinations.

We have attempted to differentiate the various factors responsible for these apparently paradoxical results, grouping them under four separate headings, according to whether they arise in the lungs, bronchi, pleura or chest wall. A brief discussion of these various factors follows:

(a) *Pulmonary factors:* Parenchymatous lesions may pass unobserved in the routine clinical-radiological examination, either because they are too small to be

diagnosed by these methods, or because they are erroneously underestimated, as in the case of emphysema and diffuse fibrosis, or because their situation is such that they remain completely hidden. The latter is most likely to occur when dealing with the left lower lobe.

Pulmonary emphysema, especially diffuse emphysema associated with fibrosis, reduces the ventilation and especially the oxygen consumption, thereby increasing the ventilation equivalent, as can be seen in the following cases: Case No. 3. Five years previously this patient had developed a tuberculous lesion of the right lung, which proved to be of a regressive nature. This produced a fibrotic retraction of the upper and lower lobes, not suspected roentgenologically, with a compensatory hyperdistension and fibrosis of the middle lobe. Under these circumstances, the right lung contributed only 13 per cent of the oxygen consumption, with a respiratory equivalent of 16.7 litres. The ventilation indices (vital capacity and minute volume of ventilation) were within normal limits. On the other hand, the left lung, notwithstanding its rather advanced lesions, accounted for 87 per cent of the oxygen intake, with a ventilation equivalent of 2.3 litres. Case 2, presenting an apparent retraction of the right lower lobe, is very similar, although the functional impairment is not so great. In case 9 the fibrotic and emphysematous changes, consequences of old tuberculous lesions, reduced the ventilation and oxygen consumption of the left lung, which accounted for only 25 per cent of the oxygen intake with a respiratory equivalent of 5.6 litres, in spite of the fact that the right lung presents an advanced lesion in its upper lobe. Other examples of this nature are found in cases 10 and 12.

These findings indicate the necessity of ruling out any possible emphysematous lesions, less noticeable, but no less important, than other more opaque lesions, before admitting that the functional capacity of one lung is superior to that of its opposite. Furthermore, great care must be taken when dealing with an apparently healthy lung, but which at one time has suffered either a hematogenous or a bronchogenic dissemination. In such cases bronchospirometry must be performed before deciding on any form of irreversible collapse therapy for the opposite lung.

(b) *Bronchial factors:* Bronchial lesions may greatly interfere with ventilation, at times completely annulling the respiratory function of an entire lung, without any traces of this functional impairment being indicated in the ordinary roentgenogram. In fact, an incomplete bronchial obstruction which blocks the respiration of its corresponding territory, is compatible with a perfectly clear lung field in the X-ray picture. This may occur in the following circumstances: (*1*) when the obstruction is of a valvular type, closed during expiration, thereby producing an emphysematous distention of the lung; (*2*) when the stenosis is sufficiently marked so as to impede the ventilation, although the lobe continues to be aerated by filtration through the small bronchial opening. We have called this mechanism "bronchial air filtration." In both of these cases the physical examination reveals that the normal breath sounds are either totally absent or very diminished, being replaced by sounds characteristic of bronchial

obstruction. Case 5 is an example of the functional exclusion of a lung caused by bronchial stenosis with "air filtration." It is probable that this condition is at least partly responsible for the functional impairment seen in cases 4, 6 and 7.

In 1936 Jacobaeus (16) published a series of cases of similar nature, drawing attention to the existence of aerated lung parenchyma, notwithstanding the presence of marked bronchial stenosis. His conclusions were based on the fact that bronchospirometry showed a slight exchange of air only with deep inspiration, as in the measurement of vital capacity. Woodruff (17) in his discussion of the article by Leiner, Pinner and Zavod (11), mentioned a case remarkable for complete lack of oxygen consumption in spite of the presence of aerated parenchyma. Recently Steele (18) published three cases studied with bronchospirometry, one of which is similar to case 9, above.

The influence of large pulmonary cavities on the bronchospirometric findings depends essentially on the size of their communication with the bronchial tree. For example, in case 8, the cavity which occupies the apex of the left lung must have had an ample bronchial communication, as shown by the fact that the drop in oxygen consumption was greater than that of the minute volume of ventilation, thus raising the ventilation equivalent to 25 litres. The opposite of this can be observed in case 11. This patient had a large cavity situated in the upper lobe, which was visibly retracted. The bronchospirometric examination revealed a marked decrease of the minute volume (4,500 cc. on the right side, 5,600 cc. on the left) without a parallel decrease of the oxygen consumption (155 and 165 cc. respectively). The right lung accounted for 45 per cent of the total oxygen consumption, with a ventilation equivalent of 2.9 litres. This indicates that the bronchus which drains the cavity is partially obstructed, allowing only a small amount of air to filter through. Cases 14 and 15, respectively, are identical to these two cases, with the exception that a large gaseous cyst was present in the former. In case 14 there was a large gaseous cyst in the left lung; bronchospirometry yielded the following results: the minute volume of ventilation was greater on the left than on the right side, while the oxygen consumption was lower. The left lung accounted for only 10 per cent of the oxygen consumption, with a ventilation equivalent of 17 litres. An ample communication existed between the cyst and the bronchial tree. Patient 15 presented a pneumonectasia, similar in size and location to the gaseous cyst of the previous case. In this instance there was no marked difference between the slight decrease in the minute volume of ventilation and that of the oxygen consumption. This is explained by the lack of ventilation of the emphysematous area.

(c) *Pleural factors:* Pleural lesions, mainly symphysis, hardening and thickening of the pleura, frequently diminish the functional value of the corresponding lung. In most cases, the oxygen consumption is particularly influenced, perhaps because of a pulmonary sclerosis of pleural origin. These lesions which are not always apparent in the roentgenogram, are frequently encountered, not only accompanying pulmonary lesions, but also in the course of an artificial pneumothorax.

The bronchospirometric findings in case 1 prove that the functional relation-

ship of both lungs was normal, notwithstanding the advanced tuberculous lesion of the left lung. This is explained by the diminished efficiency of the right lung, due to its basal pachypleuritis. Further examples of this nature are to be found in cases 4, 6, 7, 8 and 10, all of which have a poor ventilation equivalent. It is a noteworthy paradox that these lungs, in which the pleural lesions seem preponderant, have a poor ventilation equivalent, indicating that the oxygen intake is more impaired than ventilation.

(d) Finally we shall consider the influence on function caused by *changes in the chest wall.* The existence of painful phenomena, muscular atrophy, paresis or paralysis of the phrenic nerve, may reduce the efficiency of the respiratory muscles on one side of the thorax. Case 13, a patient on whom a left thoracoplasty had been performed, is a good example of how the bronchospirometric findings may be affected by the presence of a broncho-parietal fistula, that allowed entrance of air through the thoracic wall, overcompensating the oxygen consumption.

The paradoxical results of bronchospirometric exploration are not due to any inherent inefficiency or to technical errors, and therefore do not diminish its value in pulmonary practice. Conversely, rather, they increase its value by proving that the determination of the functional capacity of the lungs, based exclusively on the clinical-radiological examination, may be erroneous and should be controlled, corrected and perfected through bronchospirometric examination.

As can be seen by a perusal of the cases referred to in this paper, considerable prognostic and therapeutic data can be acquired from a thorough investigation of the functional capacity of each separate lung, which is only feasible by means of a bronchospirometric examination.

SUMMARY

Fifteen cases were selected from a group of over 400 bronchospirometries in order to point out the discrepancies between clinical-radiological and bronchospirometric examinations. The factors responsible for these apparently paradoxical results are analyzed and classified on an anatomical basis.

The advantage of a bronchospirometric examination for all patients who are to be submitted to surgical collapse therapy, and whose functional lung capacity is doubtful, is plainly indicated.

SUMARIO

De un grupo de más de 400 broncoespirometrías escogiéronse quince casos para señalar las discrepancias observadas entre los exámenes clínico-radiológicos y broncoespirométricos. Los factores a que se deben estos resultados aparentemente paradójicos son analizados y clasificados desde el punto de vista anatómico.

Queda claramente indicada la ventaja que reporta un examen broncoespirométrico en todo enfermo que va a ser sometido a la cirugía colapsoterápica y sobre cuya capacidad pulmonar funcional hay dudas.

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PROMIZOLE TREATMENT OF MILIARY TUBERCULOSIS[1,2,3]

Toxic Effects on Thyroid Gland and Maturation

LILLIAN MILGRAM, IRVING LEVITT AND MAYA S. UNNA

The sulfones promin, diasone and promizole, which have a marked influence on experimental tuberculosis of guinea pigs (1 to 6), are far less effective in clinical tuberculosis as it occurs in the adult patient (7 to 13).

We administered promizole to tuberculous children, treating 5 cases of meningitis, with no apparent effect on the course or duration of the disease. There were under observation at that time 2 children with acute generalized miliary tuberculosis. These patients were selected for further trial of the new drug, as we considered the prognosis for life to be almost as bad as that of meningitis.

We also treated with promizole the next 3 consecutive children in whom we made the same diagnosis. Then followed 2 inadequately treated cases; the sixth case was treated for twelve days, the treatment was interrupted because of possible toxemic symptoms and when treatment was to be renewed the child was taken home against advice. This child is still alive, and it is impossible to evaluate the rôle of promizole in the unusual outcome. The seventh case was treated for four weeks and medication stopped because the limited supply of promizole forbade our continuing. This patient died of tuberculous meningitis; the lumbar puncture showed abnormalities five weeks after medication was stopped. The first 5 of these children, and more particularly the first 3, are the subject of this report.

The duration of the disease at the beginning of treatment is shown in table 1. Symptoms were present for two to six weeks before the first X-ray film was taken; this first roentgenogram, in every case, showed miliary dissemination. It would appear, therefore, that the general symptoms were due largely to the hematogenous dissemination, and we have no way of dating the time of onset of the primary lesion. We can only conjecture that it preceded the clinical symptoms by at least several weeks. The interval between the first X-ray film showing miliary dissemination and the beginning of promizole administration was from three weeks to four and one-half months.

DOSAGE

Promizole was given orally in 0.5 g. capsules, in liquids or disguised in jelly, peanut butter or similar foods.

The initial dose, that is, 3 g. daily in 6 doses, was toxic for the first patient (36 pounds), who vomited repeatedly. After a period of withdrawal, she tolerated a smaller amount and during the third month she was able to take 2.5 g. We attempted, on the advice of Hinshaw and Feldman (7), to give the drug to the limit of tolerance. The second patient

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[2] Aided by a grant from the National Tuberculosis Association.

[3] Promizole was supplied through the courtesy of Parke, Davis & Company, Detroit, Michigan.

(27 pounds) took the 3 g. dose better, and in the fifth month her intake was increased to 4 g. The third patient (35 pounds) was started in October on 2 g., while the fourth (31 pounds) received amounts increased to 2 g. at the end of three weeks. Administration was then interrupted for a period because of the development of marked intestinal stasis which might have been attributable to the drug, as small intestinal atony had been found in mice and rats in toxicity studies. The fifth child, a small infant weighing only 13 pounds, was maintained constantly on 0.5 g. daily.

After several months of experience with the drug it became clear that we would have to exceed the originally contemplated six months' maximum test period. First, while the miliary lesions in the 2 first treated children were decreasing, there was much evidence of persistent infection in these children. Second, in experimental animals treated with promin, viable organisms were present in the spleen, even when there was no obvious evidence of infection (1). Third, Medlar and Sasano (3) had shown that in apparently cured animals the course of infection was reversible after treatment with promin was stopped. Further, the thyroid enlargement of children receiving the drug was disturbing and its ultimate significance uncertain. We therefore decided, on the advice of Doctor Medlar, to reduce the drug given the 3 children then under treatment to a small main-

TABLE 1

CASE	INTERVAL BETWEEN FIRST SYMPTOMS AND FIRST ROENTGENOGRAM SHOWING HEMATOGENOUS DISSEMINATION	INTERVAL BETWEEN FIRST POSITIVE ROENTGENOGRAM AND BEGINNING OF PROMIZOLE TREATMENT	INTERVAL BETWEEN FIRST SYMPTOMS AND BEGINNING OF PROMIZOLE TREATMENT
I. R. C.	6 weeks	1 month	2½ months
II. P. C.	1 month	3½ months	4½ months
III. J. A.	2 weeks	4½ months	5 months
IV. E. B.	1 month	3 weeks	1¾ months
V. R. L.	?2 weeks	1 month	1½ months

tenance dose (1 g. daily), but to give any new cases initially higher doses, which we planned to increase to the limit of tolerance, also using the blood levels as a guide. Patients placed on the maintenance dose are still receiving 1 g. daily at the time of writing.

Blood levels in the first 3 cases averaged on the higher doses 7.0, 2.3 and 4.1 mg. per cent, respectively. On the maintenance dose the average blood levels were 2.4, 1.5 and 2.7 mg. per cent.

CLINICAL COURSE

Three of the treated children are alive. Two died, one of toxemia after seven weeks, the other of meningitis, after four months of treatment.

The miliary mottling increased in the first few weeks of treatment in 2 children. In four to five months these mottlings began to recede, disappearing after a year of therapy. There was an increase in the primary lesion and its cavity in case I after promizole administration had started; then followed slow and incomplete clearing. The primary lesion of case II had two exacerbations under treatment, the second after one and one-half years, while the cavity was still present in June, 1946. Case III showed progressive clearing. The third

child early developed evidence of renal tuberculosis and spondylitis, and later, of chorioretinitis. The dissemination to kidney and spine may well have occurred at the time of the seeding in the lung.

There were no prolonged exacerbations of fever, although brief rises continued. The erythrocyte sedimentation rate reached normal levels in about a year. Tuberculin patch test was positive in 2 children after twenty-three months of treatment. The spleen ceased being palpable in the first patients within a year, while it remained very large in the third. The organ showed areas of calcification in 2. The liver could no longer be felt. No change was noted in the size of the superficial lymph nodes.

TOXIC EFFECTS

Cyanosis, slight or moderate in extent, appeared in some patients; it occurred as early as a few hours after the initial dose or much later. Cyanosis has never been noted in one of the children under prolonged treatment, but has been persistent in the other 2. By photospectrometric study, methemoglobin was found in the blood, even when no cyanosis was observed.

Vomiting occurred sporadically and frequently there was uncertainty as to whether this was due to the medication. It occurred early (within the first twenty-four hours) or was delayed until the end of the second week. In only one case was it persistent, requiring temporary discontinuance of medication. In others it was overcome by diminishing the dose.

Blood: The white blood cell count usually rose soon after starting medication. Leucopenia occurred in one case after three weeks and in another after four months, the number of cells falling in both to 3,800. After the medication was discontinued, the count rose and has since averaged 6,000 to 7,000.

Both hemoglobin and red blood cell count fell in patient III, who was very ill with tuberculosis, after nine days of treatment (to 8 g. and 2.96 million). This child then received a transfusion. The others under prolonged treatment show little adverse effect.

Skin: Pruritus occurred in case I, when medication was administered after a period of withdrawal. It persisted for one week.

Urine: The urine at times had a pink color. Occasionally it contained a reducing substance which gave an atypical sugar reaction.

Jaundice: Clinical jaundice lasted a week in case III. It cannot with certainty be considered a promizole effect, although jaundice is common with sulfone (9, 11) and sulfonamide therapy (14). There was no evidence of liver damage, nor did any develop later. The red blood cell count and hemoglobin remained unchanged during this period and gave no indication that significant hemolysis had occurred.

Thyroid gland: Thyroid enlargement appeared two to five months after administration of promizole was begun. The drug was discontinued for a month in case I, as soon as enlargement was observed, and during this period there seemed to be a slight diminution in size. In cases II and III promizole was not discontinued and the gland enlarged steadily, much more rapidly in the latter.

Thyroid extract in small doses caused slow and seemingly complete disappearance of the glandular enlargement, while 1 g. of promizole was being taken. However, when the extract was discontinued and marked enlargement recurred, larger doses have been followed by only partial diminution up to the present time. In patient II, whose thyroid was least affected, one-sixteenth of a grain prevented recurrence of enlargement.

Initial cholesterol determinations, after the gland had become palpable, were 250 mg. per cent or over in all patients. Repeated determinations, however, done before giving thyroid extract and while the patient continued to receive promizole, showed values within normal limits. Normal values were also found in patient III before his thyroid enlarged and in patient IV, whose thyroid never was felt but showed toxic changes at autopsy. The basal metabolic rate, determined in 2 cases, showed no abnormal diminution. The rate of development of carpal centres was unaffected over a period of about two years.

The thyroid gland of a child (figure 7) treated intermittently with promizole for seven weeks showed at postmortem examination the increase in cell height, diminution of colloid, hyperplasia and hyperemia characteristic of animals given this drug (15, 16). No thyroid effect occurred in adult patients treated with promizole.

In this action promizole resembles sulfaguanidine (17), thiourea and other sulfonamides (18). Promin has displayed a similar action in rats (19), and diasone has caused thyroid enlargement in a 17 year old girl (11).

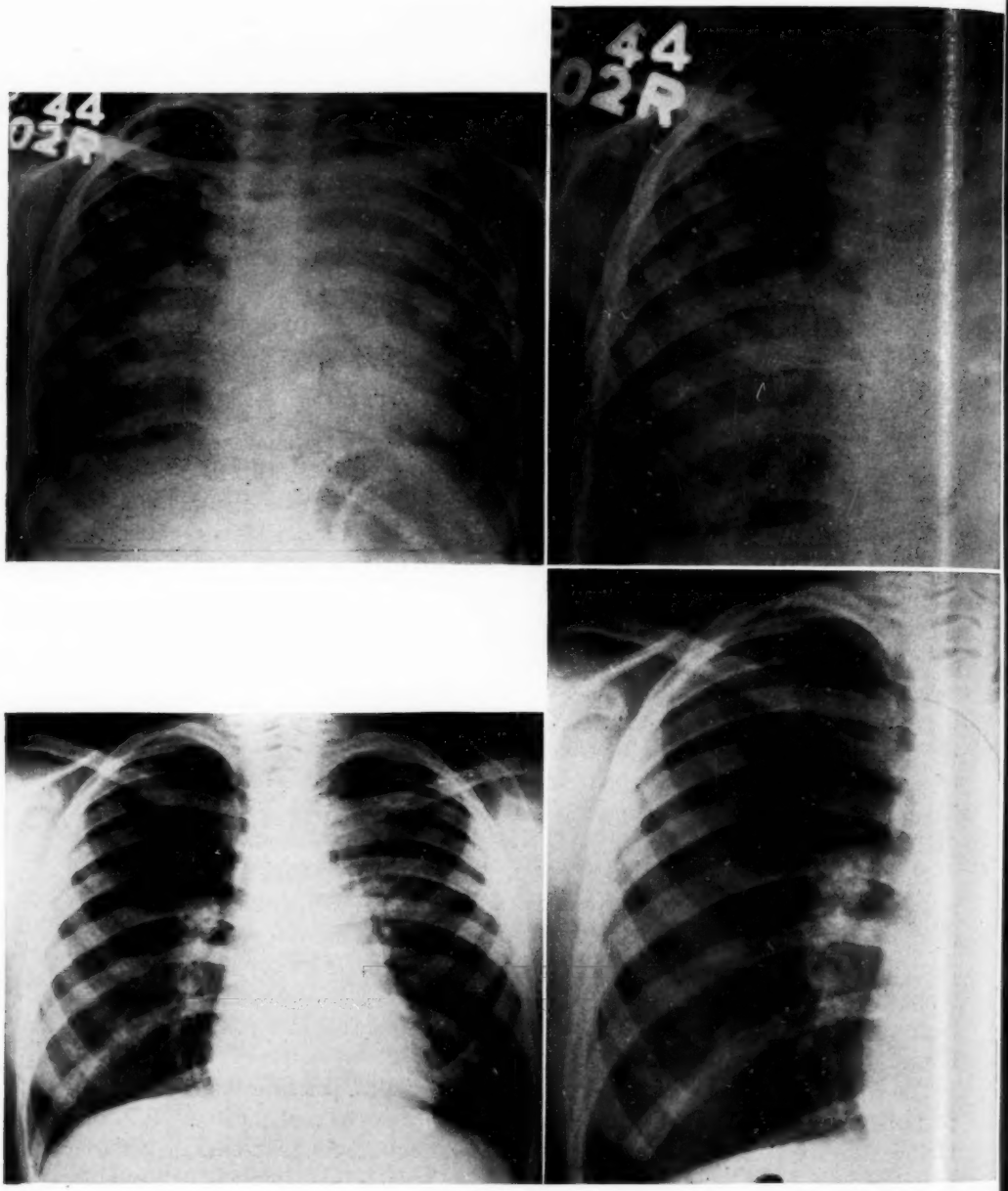
This thyroid hyperplasia is considered to be compensatory to the failure of thyroid hormone synthesis (20). Administration of thyroid extract or thyroxin corrects the defect. As for the influence of thyroid hypofunction on the course of tuberculosis, it is generally believed that cretins and myxedematous patients have a low resistance to tuberculosis (21), and it has been shown experimentally (22) that thyroidectomy has an unfavorable effect on tuberculous guinea pigs.

Maturation: Case II, treated for seven months, developed enlarged nipples and labial hair at less than 3 years of age (figure 6). The same phenomena, in more marked form, occurred in the older girl, then about 6 years old. Since then, an acneform eruption has appeared on her face. The boy has a growth of scrotal hair. There is no change in the external genitalia and vaginal epithelium is normal. Assays for the urinary 17-ketosteroids yielded elevated values in the girls, normal ones in the boy.

The effect has been on secondary sex characteristics, the skin of the face, and perhaps on body weight. There is no evidence of a true maturation. It is well known that the period of maturation is a dangerous one for tuberculosis; whether promizole can be exerting a harmful influence through this effect is questionable.

CASE HISTORIES

Case I: R. C., colored female, born 4/1/40, admitted 5/19/44. For two months, following tonsillectomy, she had fever, would not eat and complained of pain in the throat. There followed night sweats, irritability and a productive cough. She became drowsy, had headaches and photophobia. A tuberculous cousin lived with the family from Au-



FIGS. 1–2

FIG. 1a. (Upper left) Case I. June 2, 1944. Clouded left upper lung field with small cavity over second anterior rib, wide right mediastinum, large right root, mottled lung fields.

FIG. 1b. (Upper right) Detail of right lung.

FIG. 2a. (Lower left) Case I. June 6, 1946. Clouding in second left interspace, widened left mediastinum, large right root, basal streaking, mottling not seen. Breast shadow.

FIG. 2b. (Lower right) Detail of right lung.

gust, 1943 to March, 1944. She was admitted from a District Health Clinic, where her Mantoux test (0.1 mg.) (5/12/44) had been positive and an X-ray film showed a clouding of the left upper lung field and mottling through both lungs.

On admission she was well nourished, weighed 39 pounds. She had a frequent harsh cough. There were many small superficial lymph nodes, the tip of the spleen was felt, the liver was palpated a finger's breadth below the costal margin. There were dullness and inconstant râles over the left upper anterior lung field. The temperature was irregular, reaching 103° and 102°F. Hemoglobin was 11 g., white blood cells 13,800. The sedimentation rate (Cutler) was 28 mm. in one hour. X-ray films confirmed the preadmission findings (figure 1). After 6/4/44 the temperature dropped, with elevations to 101°F.

Promizole was given on 6/6/44, 3 g. daily (six times, 0.5 g.). On 6/7/44 she began vomiting; cyanosis and pallor were noted; on 6/12/44 she became delirious and had choreiform motions of the arms and legs. Promizole was stopped. Her condition cleared rapidly and on 6/22/44 the drug was given again, 2 g. daily. The sedimentation rate remained high, 34 mm. On X-ray films the mottlings increased in size for one and a half months after treatment began, while the clouding extended and the cavity reached a maximum of 20 x 25 mm. The temperature meanwhile fell to lower levels, with peaks below 100.5°F. After the middle of August, she gained weight steadily. On 9/15/44 the intake of promizole was increased to 2.5 g. daily.

The X-ray of 10/13/44 showed the mottlings to be smaller. Acid-fast bacilli were found on smear of the gastric contents for the first time on 9/25/44 and again on 11/22/44, but not afterwards.

On 11/7/44 the thyroid gland was seen to be very large and promizole was discontinued. In October the red blood cell count had fallen to 3.0 million and the white to 6,500. Folic acid was given, starting 11/9/44. However, by 11/20/44 the white cell count fell to a low of 3,800. After that there was a sharp upward swing in the blood count. On 12/7/44 the patient was put on a low, maintenance dose of 1 g. of promizole and later (1/3/45) she was given thyroid extract (grain $\frac{1}{3}$). On this medication the gland slowly decreased in size.

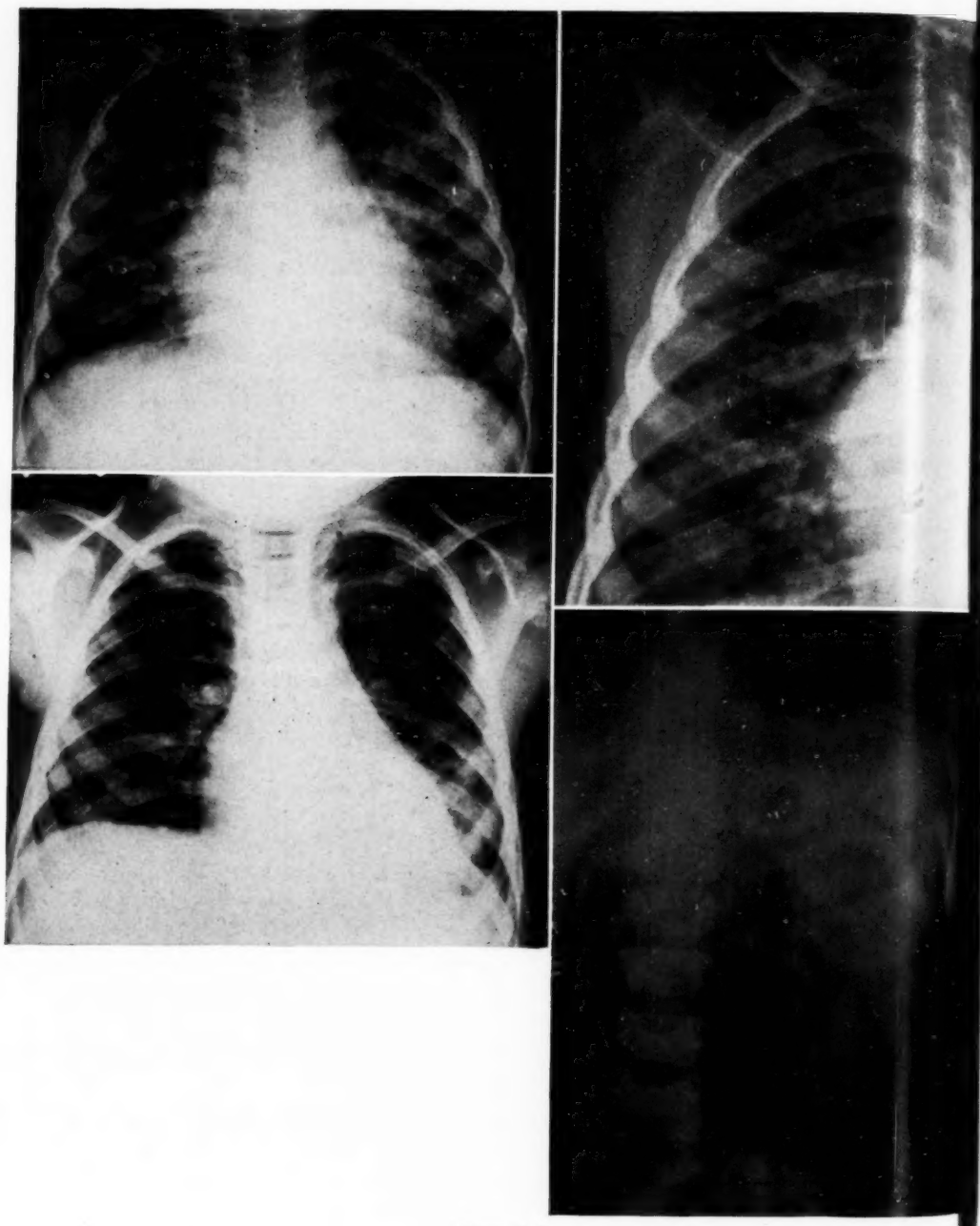
In April and May, 1945, the miliary nodules were poorly seen on X-ray films, the spleen was now barely palpable. There was partial clearing of the left upper lung and the cavity could not be seen nor were physical signs present. In July the sedimentation rate fell to 14 mm. The temperature now rarely rose over 100°F. The thyroid gland was no longer felt and thyroid medication was discontinued. On 8/6/45 the patient was allowed to go home, to be kept in bed.

At home she gained weight rapidly. A moderate enlargement of the thyroid gland was once more observed on 9/6/45. Thyroid medication in increasing doses resulted in incomplete diminution of the gland. There was very slight cyanosis. Liver and spleen were no longer felt, perhaps because of the obesity.

In January, 1946, there began an enlargement of the nipples, with the appearance finally of breast nodules. Urine assay[4] (2/8 to 2/11/46) showed an increase in the 17-ketosteroids, 3.1 mg. daily. The vaginal epithelium was normal. At the end of May there appeared on her face an acneform eruption, with a moderate number of comedones.

Tuberculin patch test 5/29/46 was positive. Her X-ray film (figure 2) showed an irregular widening of the left mediastinal shadow and clouding in the second interspace

[4] Urine assays for 17-ketosteroids were done in these cases by Dr. Konrad Dobreiner, vaginal epithelium examination by Dr. Ethel Dana, and pubic hair examination by Dr. James B. Hamilton.



FIGS. 3–5

FIG. 3a. (Upper left) Case II. May 17, 1944. Cavity in fourth left interspace, slightly enlarged roots, mottled lung fields.

FIG. 3b. (Upper right) Detail of right lung.

FIG. 4. (Lower left) Case II. March 15, 1946. Clouding and highlight left base, slight enlargement right root, mottling not seen. Small densities left first and second interspaces.

FIG. 5. (Lower right) Case III. Large spleen, containing areas of calcification.

without definite calcification. Blood examination: hemoglobin 11.5 g. per cent, white blood cells 5,100.

Case II: P. C., colored female, born 2/23/42, admitted 2/12/44 from a District Health Clinic, where she had been examined as a contact to her tuberculous mother, who was hospitalized 1/7/44. Our patient's Mantoux test (2/7/44) was positive. For a month before admission she had persistent fever to 102°F., anorexia, loss of weight, irritability and cough. On examination she was in a fair nutritional state; she weighed 22 pounds and did not look ill. There was a generalized micro-lymphadenopathy. The liver was felt two fingers' breadth below the costal margin, the spleen was not palpable. The temperature reached 102°F. On 2/15/44 she vomited, was listless and drowsy; a lumbar puncture gave negative findings. For five weeks after admission she ran an irregular fever, to 101° and 102°F., which then subsided to normal with rare rises over 100°F. Her sedimentation rate on admission was 28 mm. (Cutler) in one hour, hemoglobin 9.5 g., white cell count 20,200. Admission X-ray films showed enlargement of both lung roots, some clouding of the left base adjacent to the heart containing a vaguely seen cavity and mottling throughout the lung fields.

During the three and one half months before therapy started the mottlings increased in size and the cavity became more definite (figure 3). The spleen became palpable. However, her general condition improved, she gained weight, her sedimentation rate fell to 14 mm. and the white blood count to 12,200.

Promizole was given on 6/6/44, 3 g. daily (six times, 0.5 g.). Her X-ray films continued to show the initial abnormalities, but in August the mottlings appeared smaller. The sedimentation rate became more rapid in August (24 mm.) and remained high through October. On 10/11/44 the temperature rose to 102°F.; medium moist râles, dulness and diminished breath sounds were found in the lower left chest posteriorly. X-ray films showed an extension of the lesion. Promizole dosage was increased on 10/18/44 to 4 g. per day. On 11/21/44 acid-fast bacilli were for the first and only time found on smear in the gastric contents. Physical signs in the left base persisted. However, in November it was definite that the lung mottlings were smaller.

Toward the end of November there was noted a very slight enlargement of the thyroid isthmus, and on 12/1/44, in accordance with the new plan of treatment, the promizole intake was decreased to 1.0 g. The thyroid gland increased to a moderate size. On 12/26/44 prominence of the nipples was noted (figure 6) and a slight hairiness of the labia majora. Urine assay (1/16 to 1/22/45) showed a slight increase in the 17-ketosteroids, 1.9 mg. daily. On 2/16/45 administration of thyroid extract was begun and continued until July, when the gland could no longer be felt. The nipple enlargement and labial hair remained unaltered.

The mottlings became barely visible on X-ray films after 1/15/45 and the chest signs disappeared. After January the spleen was no longer felt and early in March two areas of calcification were well seen in that organ. In March there were no definite mottlings on X-ray films. The liver was last felt in May.

Her course has been uneventful since. She stays in bed, eats and plays at table. She has gained slowly in weight. The thyroid isthmus again became palpable in February. The basal metabolic rate (3/8/45) was plus 23 per cent. On a very small thyroid intake the gland has remained small. Tuberculin patch test (5/26/45) was positive. X-ray films (6/10/46) showed about a dozen small densities, persistent slight clouding on the left with its highlight (compare figure 4). Blood examination: hemoglobin 9 g., white blood count 7,350.

Case III: J. A., Porto Rican male, born 4/5/38, admitted to Bellevue Hospital 8/31/44. History dated to 5/12/44, when he passed a restless night and seemed warm. The next day he received a routine injection of diphtheria toxoid, which was followed by a rise of temperature to 105°F. Fever, chills and sweats, and a nonproductive cough continued for two weeks. He was admitted to another hospital. He was described as being pale and malnourished, weighing 30 pounds. The liver extended one finger's breadth below the costal margin and the spleen two fingers. Mantoux test with 0.01 mg. OT was positive. X-ray film of the chest (5/27/44) showed miliary mottling through both lungs and an enlarged right root. In later films there was an increase in the size of the mottlings, enlargement of both roots and widening of the mediastinal shadow to the right. On 8/18/44 a roentgenogram showed a moderate right pleural effusion. During the period of hospitalization the temperature ranged to 104°F., with almost normal intervals. By

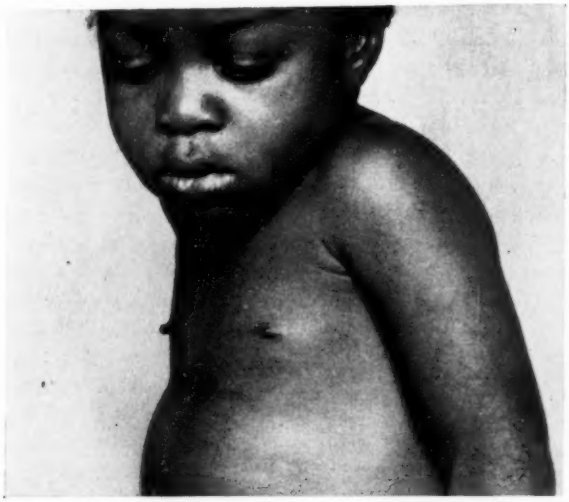


FIG. 6. Case II. Nipple prominence after seven months of treatment

the time of transfer he had gained weight and the temperature rose not above 101°F. On 9/29/44 he became acutely ill with a left-sided pleural effusion and on 10/11/44 developed abdominal tenderness. At this point, 10/14/44, promizole was given (0.5 g. every six hours). The abdominal picture progressed, he vomited and refused food. It was noted that the spleen had become enlarged and tender, extending down to the umbilicus, the liver was now 3 cm. below the costal margin. He was cyanotic and dyspneic. By 10/27/44, however, his general condition began to improve, although abdominal tenderness became more marked over the splenic area. On 11/6/44, because of a fall of the white blood count to 3,800, promizole was discontinued. By the middle of November, abdominal symptoms disappeared and he gained weight. Chest X-ray films showed an increase in the mottling. On 10/23/44 a few white blood cells were found in the urine, slight abnormality persisted and on 12/5/44 culture and smear showed acid-fast bacilli.

Promizole was started again in small dosage on 12/6/44. On 12/19/44 the thyroid isthmus was barely palpable. Icterus of the sclerae was observed on 12/21/44; the icterus index was 20; repeated a week later, the icterus index had fallen to 9.6.

By 2/14/45 the thyroid gland enlarged further, and he was given thyroid extract.

The basal metabolic rate on 3/10/45 was minus 8.5 per cent. Chest roentgenograms of 3/2/45 showed a questionable diminution in size of the miliary nodules. Films showed increasing areas of calcification in the spleen, first visible in January (figure 5). On 3/4/45, with a slight febrile rise, he complained of back pain. Films of the spine revealed spondylitis of the eleventh and twelfth dorsal vertebrae. A review of previous films showed that this process had begun on 1/3/45 and possibly as early as 11/8/44. On 3/19/45 a positive smear of the gastric contents was reported; after that no acid-fast bacilli were found on smear or culture. In August the fundi showed evidence of bilateral old and recent chorioretinitis; the last negative examination had been made in March. Urinary findings continued and urine cultures were repeatedly positive for tubercle bacilli, the last on 10/7/45. A retrograde pyelogram on 1/14/46 revealed normal pelves and calyces.

Films taken 10/8/45 showed the miliary nodules in the lung to be no longer definitely visible. The urinary sediment continued to contain white blood cells; however, the urine culture on 2/8/46 was negative for tubercle bacilli. The spine lesion was progressive. His weight was stationary. He was slightly cyanotic, his thyroid was large, there was a sparse growth of scrotal hair. A normal serum bilirubin, 0.76 per cent, gave no indication of hemolysis, while his blood examination on 6/3/46 showed 10.5 g. hemoglobin, 5,400 white blood cells, 62 per cent polymorphonuclear leucocytes.

Case IV: E. B., colored male, born in June, 1942, admitted to Bellevue Hospital 12/16/44. The history dated back to about 10/25/44, when he developed a cold with a cough, became anorexic and irritable, and finally grew febrile and dyspneic. He had been in close contact with a 17 year old tuberculous sister. On 11/24/44 he was admitted to another hospital, where he was at first thought to have an asthmatic attack. The Mantoux test (0.1 mg.) was positive. The chest film showed a nodular area of clouding in the seventh right anterior interspace, an enlarged right root, thickened right pleura, widened mediastinum and mottled lung fields.

On transfer to Bellevue he was in respiratory distress. There was an audible wheeze with a high-pitched paroxysmal cough and suprasternal and epigastric retraction. The heart rate was 166 per minute, the liver 10 cm. below the costal margin, the spleen just palpable and the abdomen markedly distended. There were dulness and diminished breath sounds through the right chest with bronchial breathing posteriorly.

Promizole was first given on 12/19/44 (1.0 g. daily) and increased by 1/10/45 to 2.0 g. The child continued much the same, his temperature rising to 102° to 104°F. daily. His chest signs progressed, showers of resonant râles were heard over both bases. On 1/13/45, because of even more marked abdominal distension, the promizole was discontinued, but as the abdominal signs were unaffected, the latter was given again on 1/24/45 (0.5 g.) and increased to 1.0 g. daily. In the chest films the mottlings seemed a little larger and on 1/8/45 a cavity, 6 x 6 mm., was seen in the area of right basal clouding. His cervical nodes enlarged, the liver increased in size and amphoric breath sounds were heard over the right base and axilla. There were no signs of meningitis. He became somewhat more drowsy and irritable and slightly cyanotic. Spinal fluid aspirated postmortem contained no tubercle bacilli on smear or culture.

Autopsy, performed by Dr. Carter Alexander and Dr. John W. Hall, showed primary tuberculosis, with the primary lung component in the lower portion of the right lower lobe; caseous tuberculous pneumonia of the right lower lobe; tuberculosis of the tracheobronchial lymph nodes; tuberculous empyema and fibrous pleural adhesions right; miliary tuberculosis of the lungs, liver, spleen, pericardium and kidney; early tuberculous lepto-

meningitis; hyperplasia of the thyroid gland. The gross and microscopic description of the thyroid gland follows: "The thyroid is normal in size, shape and consistency. Its cut-surface is reddish brown and does not appear to contain colloid. On microscopic examination the acini show considerable variation in size and shape, but most are smaller than normal. Most of the follicles are lined by tall columnar epithelium and in the larger acini epithelial pegs are present. Only a rare acinus contains colloid. The stroma is normal in amount, but within it the capillaries reveal marked congestion." (Figure 7.)

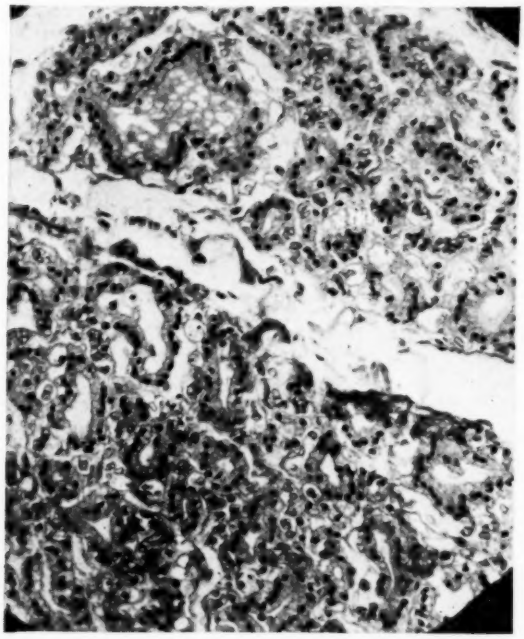


FIG. 7. Thyroid gland of case IV, who received 43 g. of promizole in seven weeks. Most of the follicles are lined by tall columnar epithelium. Only a rare acinus contains colloid.

Case V: R. L., Porto Rican male, born 8/17/44, admitted on 1/23/45 to the Ear, Nose and Throat Service, Bellevue Hospital, with a one-day history of fever and irritability and a discharging ear. In spite of a mastoidectomy and a contralateral myringotomy, the temperature on 2/22/45 reached 105.4°F. He became croupy and his respirations rapid and grunting. On 2/24/45 there were râles and bronchial breath sounds over the right upper chest and a clouding of the right upper lobe was seen on the X-ray film. Pneumococcus type-XIV was obtained repeatedly on nose and throat cultures and also on ear culture. An X-ray film of 2/28/45 showed an effusion in the right chest. By 3/5/45 the effusion had cleared and there was a haziness of the right upper lobe region with nodular areas of clouding (4 mm. to 8 mm.) in the first three interspaces; there was a widening of the right mediastinum. The fever disappeared, but on 3/8/45 his temperature rose again to 101°F. Mantoux test (0.1 mg.) was positive. Study of the earlier X-ray films (2/24/45 and later) showed a fine mottling. The clinical impression was that this tuberculous infant had also suffered from mastoiditis and pneumonia in which pneumococcus type-XIV was at least one of the pathogens.

On 3/22/45 promizole administration was begun (0.5 g. daily). By this time the nodu-

lar lesions on the right had enlarged and the mottling had increased. He was extremely irritable, weak and thin, and weighed 13 pounds. He breathed rapidly and coughed on being disturbed. It was a paroxysmal cough, often metallic in quality.

The infant improved clinically, ate well and made a slight weight gain. His ears stopped discharging, his temperature was only occasionally febrile. Slight cyanosis was observed 4/27/45; the thyroid gland was not palpable. Gastric examinations were negative for tubercle bacilli on smear and culture. On 6/9/45 a new febrile period began, both ears again discharged, and he became more irritable. Lumbar puncture was done on 7/14/45 and the spinal fluid proved to be normal. X-ray films showed constant progression, his condition deteriorated, râles were heard bilaterally in the chest, his respiratory distress increased until he seemed almost frantic. There was no vomiting. Neurological signs were absent until the day of death (8/1/45) when there were nuchal rigidity, periods of respiratory apnea and, just before death, convulsive movements of one lower extremity. Lumbar puncture: pressure 250 mm., 30 lymphocytes, sugar 79.5, Pandy negative, cultures negative. Autopsy was not done.

DISCUSSION

Prognosis of miliary tuberculosis; significance of results: Three of 5 consecutive cases of acute generalized miliary tuberculosis treated with promizole are alive twenty-four to twenty-seven months after their miliary lesions were first seen and these lesions have receded according to X-ray examination. Is this unusual? In the opinion of many experienced clinicians, it is. Amberson (23) said of acute miliary tuberculosis, "The prognosis is uniformly hopeless and treatment unavailing." Pinner (24) in 1945 wrote, "A few cases are on record in which a miliary seeding resorbed and left roentgenologically normal lung fields."

The literature contains many reports, commonly of isolated cases, of chronic miliary tuberculosis, that is, of patients outliving the usual course of six to ten weeks. Hoyle and Vaizey (25) analyzed 10 patients of their own who lived more than three months and collected 110 additional cases from the literature. For comparison with our patients, one should select cases similar to them, that is, acute miliary disseminations in children which occurred when the primary lesion was fresh and which retrogressed, the children surviving for fairly long periods. This eliminates cases with larger than miliary lesions or with disseminated calcification when first seen. It does not exclude patients who fail to present the acute clinical picture: there is a difference of opinion about the significance of the acute onset. Hoyle and Vaizey found the onset to be more acute in those who survived a shorter time; and conversely, less acute in those who went on to recovery. This had been essentially the opinion of Assmann (26) and of Hein (27). However, Fish (28), as well as van Creveld and Huët (29), thought the prognosis unaffected by the acuteness of the onset. Our patients all had an acute onset.

Engel (30), on a service which every year saw 20 to 25 cases of tuberculous meningitis in children, says that in fifteen years of experience he saw only one case of survival from miliary tuberculosis. Duken (31) reported apparent recovery from miliary tuberculosis in 2 or perhaps 3 children. Similarly, Armand-Delille and his coworkers (32) described altogether 4 cases of miliary tuberculosis with apparent recovery seen at the Hôspital Hérold, Paris.

Wallgren (33) stated that, of 84 cases diagnosed clinically and roentgenologi-

cally as acute miliary tuberculosis at Gothenburg within a period of fifteen years, 5 recovered (one had clinically acute miliary tuberculosis, in 4 there were no clinical symptoms at all). Our experience has been as follows: in the past fifteen years we have had only 2 cases in children under 13 years resembling these. The first, admitted in 1932, cleared most of his miliary lesions, sickened of acute tuberculous bronchopneumonia and died twenty-two months after the onset of miliary tuberculosis. This case has been previously published (34, 35). A second child, observed for twenty-three months, whose miliary lesions have shown marked regression, is the patient who received promizole for twelve days.

There are observers, however, who have more frequently met with recovered cases. Fish (28) reported 4 apparent recoveries, 3 of whom had been treated with a gold salt, *Solganol-B oleosum*. Roberts and Nassau (36) saw 4 children with apparent recovery from miliary tuberculosis at the time of writing, and a fifth who died after eighteen months. One of these children apparently disseminated following a hip injury; no primary focus in the lung is mentioned. Van Creveld and Huët treated, in a sixteen-year period, 12 children under 13 years of age, diagnosed as chronic miliary tuberculosis; all but one recovered and that patient lived over two years. The first impression from these figures is that acute miliary tuberculosis has an excellent prognosis, yet an analysis of this interesting paper makes it clear that most of the cases were already of moderate or long duration when first observed by the authors: 3 were of one to three years' duration, 3 of six to ten months', as measured by X-ray detection. Of the remaining 6 cases, 5 were diagnosed at the sanatorium and one was of four months' duration when admitted.

The proportion of recoveries among the total number of acute miliary cases is given only by Wallgren. From his statement that he saw 20 to 25 cases of tuberculous meningitis annually, it is evident that Engel also saw a correspondingly large number of acute miliary tuberculosis.

Our final impression is that our results, though based on a very small group, indicate that the drug used has a favorable action.

Possible sites of drug action: In attempting to explain the apparent prolongation of life up to this time, one should be clear as to the usual causes of death. For convenience one may refer to Hoyle and Vaizey's analysis (25). Their group I (died within six months) consisted of 13 cases. Eight of these died of meningitis, 3 of toxemia due to the acute dissemination, one of organ tuberculosis, the last of septic bronchopneumonia. In these the clinical course was one of steady deterioration with acute tuberculous meningitis as a common terminal event. Of their group II (died in over six months) the typical picture was one of remissions and exacerbations. Of 33 cases, 14 died of meningitis, 9 of toxemia due to miliary disease, 7 of organ tuberculosis and 3 of congestive heart failure.

After a prolonged course, postmortem examinations show tubercles of various ages in different organs, with a final terminal miliary spread as well as a frequent meningitis. Most investigators attribute this picture to repeated hematogenous dissemination of tubercle bacilli. A few are of the opinion that the dissemination of toxins also may give the picture of miliary tuberculosis (37, 38) or lead to exacerbations (39). Rich and McCordock (40) believe that the terminal menin-

gitis is not due to acute miliary dissemination, but that it is the end result of the progression of some old tuberculous focus adjacent to the meninges.

It would seem that a drug effective against this disease must, therefore, act to prevent dissemination and to limit local progression.

The slight effect of promizole on tuberculosis in the adult would not have led one to anticipate a striking influence on our patients. Yet in experimental guinea pig tuberculosis the drug had a marked action in causing retrogression of lesions. It may be that in our children the comparatively recent primary lesions in lung and lymph nodes, with the miliary dissemination from them, resemble the early experimental tuberculosis of the guinea pig at the site of inoculation and in the axillary or inguinal nodes, with their resulting acute hematogenous dissemination, and that this partly explains the similarity in therapeutic results. In the animals these primary lesions seemed more resistant to treatment with the sulfones than did the hematogenous visceral lesions (1, 6). In this respect also there appears to be a similarity to the response in our patients.

Some factors involved in therapeutic failures: The 2 children who died differed from the survivors in some respects which are perhaps significant. First, only they had clinical signs of tracheobronchial obstruction when administration of the drug was begun. This may have been associated in them with more bronchogenic dissemination than occurred in the others. Second, age may have been a factor, as one was by far the youngest, 7 months, and the other 2 years 6 months, as compared with 2 years 4 months, 4 years 2 months, and 6 years 6 months of the survivors. Third, duration of the disease before treatment may have been important. If we compare the intervals between the first symptoms and the start of chemotherapy, this is for the survivors four and one-half months, five months, two and one-half months, and for the deceased one and one-half months. It appears that 2 of the cases doing well *had already survived the usual duration of acute miliary tuberculosis, and they may therefore have had a better prognosis at the start of treatment than the cases of shorter duration.* On the other hand, among guinea pigs treated with promizole, a higher mortality occurred when treatment after experimental infection was delayed (6). Fourth, dosage may have been a factor. After three weeks of treatment, the drug was discontinued for eleven days in case IV. While under treatment his average blood levels (0.8 mg. per cent) were lower than the other children's. However, blood levels on the fifth child, who died after four and one-half months of therapy, averaged 2 mg. per cent, and were similar to those of patient II on her original high dosage.

SUMMARY

Five consecutive cases of acute generalized miliary tuberculosis in children were treated with promizole. Three have survived twenty-four to twenty-seven months since the diagnosis was made. It is rare to have a child survive as long as this.

The primary chest lesions cleared very slowly and incompletely. Kidney and spine lesions appeared and progressed under continuous drug administration.

Promizole has bizarre toxic effects on the thyroid gland, breasts and genital hair. These are more likely to appear after prolonged administration.

SUMARIO

Cinco casos consecutivos de granulia aguda en niños fueron tratados con promizol, habiendo sobrevivido tres de ellos de veinticuatro a veintisiete meses desde que se hizo el diagnóstico. Es raro que un niño sobreviva todo ese tiempo.

Las lesiones torácicas primarias desaparecieron con mucha lentitud y en forma incompleta. Se presentaron lesiones renales y raquídeas que avanzaron aun mientras se administraba la droga.

El promizol provoca en el tiroides, mamas y vello genital, efectos torácicos peculiares que son más susceptibles de aparecer cuando la administración es prolongada.

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ULMONARY TUBERCULOSIS AND SEASON OF BIRTH

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INTRODUCTION

Numerous studies have been made concerning the relationship between month and season of birth and psychological or physiological factors in human development. Data have been presented to show that children born in summer or autumn are heavier than those born in spring or winter (1). Studies of intelligence and season of birth have indicated that children born in warm months tend to have higher intelligence scores than those born in winter months (2). Huntington (3) has discussed the relation of season of birth with many factors: genius, length of life, insanity, disease. He discusses the relation between season of birth and tuberculosis. He concludes (4) that persons who suffer from tuberculosis show an unusual number of births during what is, generally, the most favorable season of birth, "late winter or early spring—February or March." He explains this trend in the following words:

> "The fact that this occurs at the season when the births of eminent leaders are most numerous furnishes strong, though unexpected, evidence as to the potency of the basic animal rhythm of reproduction. It apparently indicates that when the reproductive urge reaches its height in May or June two things occur. First, on the average the children who are then conceived are stronger and longer-lived than their brothers and sisters who are conceived at other seasons. This explains the high proportion of births of geniuses, or rather of persons whose innate ability finds expression in activities which lead to fame. True geniuses may be equally numerous at other seasons. Second, people who are emotionally or intellectually weak are especially likely to yield to the sexual stimulation which marks the chief season of reproduction. Such parents presumably are responsible for a large percentage of the persons who become criminals or suffer from insanity. Third, physically weak people who usually are not able to produce children may become parents under the stimulus of the primitive breeding season. Their children are probably especially susceptible to tuberculosis as well as to the influences which lead to crime and insanity."

Besides the direct factors of climate and weather, Huntington (5) cites several indirect factors which he considers as influences upon season of birth. These are factors whose effects operate through physiological, cultural and sociological conditions.

Tuberculosis is one disease afflicting mankind which has been studied in association with all these factors, but most often with climatic, meteorological and geographical factors. It is the one disease whose "cure" has been popularly, as well as medically, associated with variations in climate and season. An occasional article has been presented in which the course of the disease in patients under care has been studied in relation to the time of year and climatic changes associated with the seasons.

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Bushnell (6) states that:

"In large tuberculosis hospitals it is not unusual to see a group of far-advanced patients carried off at the rate of one, two or three a day when the conditions of weather are particularly trying, while at other periods of the year there may be no deaths for weeks at a time."

Clayson (7), reporting on 41 cases of pulmonary tuberculosis, states that:

"... there was a tendency for the sputum to be more copious during the months of February, March and April (or for part of that time) than at any other season of the year ... It thus appears that in pulmonary tuberculosis the softening of lesions takes place most commonly in the months of February, March and April."

Petersen (8) reports on a study by Browning and Ellsworth. He says:

"Browning and Ellsworth observed that the period of the equinox is more difficult for the tubercular patient living in the Los Angeles area, ... Second, he (Browning) observed that the greater the variability, that is, the suddenness and frequency of weather change, the more pronounced the clinical effect and, furthermore, that greater variability was apt to occur from the fifteenth of March to the first of April and from the middle of September to the 5th of October in the Los Angeles region, that is, in the spring and in the autumn."

In another article, Petersen (9) makes the following statement, in which he summarizes many of his observations on tuberculosis and meteorological disturbances:

"The trend to activation of tuberculosis observed in the late winter and spring is associated with the general tendency to increased catabolism evident in normal individuals as well as patients studied. The lowering of the blood pH (relative acidity) and of the blood pressure (vascular and general cellular fatigue) along with the increase in capillary permeability give objective evidence that resistance to tuberculous extension decreases with organic (tissue) fatigue. This organic fatigue results from the loss of buffers, vitamins and essential mineral and organic constituents, incidental to the repetition of environmental impact of the severe meteorological turbulence of the late winter and spring. Basically it must be considered from the point of view of an energy deficit."

In still another article, Petersen (10) generalizes his theories to all patients, not just the tuberculous.

"... the human organism is constantly pendulating in a biological rhythm that is largely conditioned by the atmosphere, though obviously every change in environmental conditions, no matter what their origin, will in some degree require adjustment and to this degree influence a labile focus, whether tuberculous in origin or not. ...

"The environmental situation is never repeated for any individual organism that exists in an unstable atmosphere such as ours. Consequently each patient must be studied individually."

PURPOSE OF PRESENT STUDY

In the present study the relationship between season of birth and pulmonary tuberculosis is discussed. A method of analysis is used which is considerably more detailed than that usually presented. If, as Cobbett (11) states regarding tuberculosis, "The seed comes to all; it is the soil which determines whether or no it shall germinate and grow to maturity," then it is possible that the soil may be more fertile at certain times of the year than at others. Huntington stresses the conception date in his analyses. In the case of tuberculosis, the period of birth may be more important, if, as Fishberg (12) observes, "the new-born infant is invariably free from tuberculosis, indicating that infection, if it occurs at all, always takes place after birth."

This is primarily a statistical report to the medical profession. The foregoing discussion of the literature is intended merely as an attempt to coördinate some of the pertinent studies on the subject as a back-drop for the numerical data.

DESCRIPTION OF SOURCE DATA

The present sample was taken from the files of the Bureau of Tuberculosis in the Board of Health in New York City. Only the files for deceased patients were used. Every card from which the exact date of birth could be obtained was included in the sample, yielding about one-sixth the total file, or about 10,000 cards. Birth-dates of persons born in the Southern Hemisphere were automatically omitted.

These cards were sorted so that only cases where the cause of death was given as pulmonary tuberculosis were used. Cards giving any other type of tuberculosis or listing any complication with the pulmonary tuberculosis were discarded. Furthermore, only cards which recorded the date of death for the seven years 1936 through 1942, inclusive, were used. Records for other years were not complete.

After all these discards were made from the original sample, the final group consisted of 5,986[2] cases. This is the group from which the following statistics were derived.

The range of birth-dates in the group is approximately ninety years.

Some vital statistics: Of the 5,986 cases, 62 per cent were males and 38 per cent were females. The proportions according to color were as follows: 70.6 per cent were white; 28.6 per cent were colored (black or mulatto); 0.8 per cent were yellow or red. A break-down by sex and color shows an interesting difference between the white and colored groups. Whereas 66.4 per cent of the whites were males, as against 33.6 per cent for females, among the colored people the proportions were very close: 50.3 per cent males and 49.7 per cent females.

Method of analysis: A distribution of the date of birth throughout the calendar year was made for the entire group. In other words, the 5,986 cases were distributed by date of birth, from January 1 through December 31, regardless of the year of birth. In this way, we had immediately available the number of births

[2] Later, in order to simplify calculations, 4 cases were excluded because they fell on February 29, and did not vary in frequency from the normal expectancy.

on any given day of the calendar year, or on any group of days. This original distribution is the source of our statistical calculations, and the method employed made possible the detailed seasonal analyses reported here. This point is stressed because very few discussions of season of birth, in any field, employ this technique. Yet, it is a necessary one for complete and accurate study.

Furthermore, this type of basic distribution, besides requiring utmost accuracy in birth-dates, makes possible analyses on the basis of the true calendar of the seasons, as defined by the astronomical delimitations of solstices and equinoxes.

In all season of birth studies, much emphasis has been placed on weather and climatic factors, whether directly or by implication, such as the grouping into cold and warm months. Yet, the studies have used a method of analysis which is not fundamentally accurate. The civil calendar of months does not define limits of season, except very vaguely. Whether climatic and meteorological factors are the basic causes of the variations reported or not, a more accurate calendar base is necessary for such discussions.

It was for this reason that the report on intelligence and personality factors by Forlano and Ehrlich (13) used a dual calendar basis. The monthly analysis was made for basic comparisons with other studies. The second analysis was made on the basis of the astronomical calendar for the seasons.

And, the detailed day-to-day distribution yields a third advantage. It makes it possible for us to analyze the data according to periods smaller than the complete season, or even month, if such periods should warrant this approach.

All three methods were found useful in the present study.

THE STATISTICAL RESULTS

The months: Our first analysis was the most obvious, by months of the calendar year. The results are summarized in table 1.

The absolute frequencies reported in table 1 cannot be interpreted directly because the number of days per month varies. The mean daily rate corrects this discrepancy and places each month in its proper relative rank. It will be noted from the table that May has the lowest mean daily rate, while August and September have the two highest daily rates. The last column of the table gives the standard deviation of the means for each month. It is used to determine the reliability of the differences between means for any two months. The difference of 2.6 and 2.8 between the means of May and August or September are statistically significant differences. Between May and August, the critical ratio is 2.55. Between May and September, the critical ratio is 2.77. A critical ratio of 2.5 or more is considered statistically significant, indicating that the differences between the means observed are due to factors other than chance.

The seasons: By dividing our original distribution according to the astronomical seasons, we were able to make a comparison between the actual cold and warm periods of the year. The solstices occur usually on June 22 for summer, and December 22 for winter. The equinoxes occur on March 21 for spring, and September 24 for autumn. Spring, therefore, includes the ninety-three days from March 21 through June 21; summer includes the ninety-four days from June

22 through September 23; autumn includes the eighty-nine days from September 24 through December 21; and winter includes the eighty-nine days from December 22 through March 20.

Table 2 summarizes the statistical data obtained by these seasonal groupings.

From table 2 it will be seen that spring has the lowest and winter the highest mean daily rate. This yields a critical ratio of 2.32, a figure somewhat lower

TABLE 1

Birth-month of persons dying from pulmonary tuberculosis in New York City

MONTH	FREQUENCY	MEAN DAILY RATE	STANDARD DEVIATION
January	479	15.5	6.9
February	481*	17.2	5.2
March	520	16.8	5.6
April	486	16.2	5.0
May	462	14.9	4.3
June	492	16.4	5.2
July	492	15.9	5.4
August	542	17.5	3.7
September	531	17.7	3.6
October	482	15.5	3.8
November	495	16.5	5.4
December	520	16.8	5.5
Total	5,982	16.4	5.1

* Frequency equals 485 when February 29 is included.

TABLE 2

Season of birth of persons dying from pulmonary tuberculosis in New York City

SEASON	FREQUENCY	MEAN DAILY RATE	STANDARD DEVIATION	NUMBER OF DAYS
Spring	1,431	15.4	4.6	93
Summer	1,596	17.0	4.7	94
Autumn	1,416	15.9	4.5	89
Winter	1,539	17.3	6.3	89
Spring and autumn	2,847	15.6	4.7	182
Summer and winter	3,135	17.1	5.7	183

than the acceptable ratio for statistical significance. But, the difference in mean daily rate for spring and autumn is very slight, just as the difference between the mean daily rates for summer and winter is slight. So, we combined spring and autumn and compared these two with the combination of summer and winter. The difference between the means obtained by this combination is statistically significant. The mean difference is 2.73 times its standard error.

The smaller areas: Tables 1 and 2 give a generalized picture of the seasonal distribution, which remains vague because it is so generalized. From them we are

tempted to arrive at contradictory conclusions: (*1*) that persons born during the month of May are least likely to die from pulmonary tuberculosis, and that those born in August and September are most likely to die from it; and (*2*) that it is the winter period which is least favorable, with the summer in second place, while spring retains its favorable position.

Statistically significant differences are derived from means of samples. Very often, means level off wide variations within the sample, which become lost in overlarge groupings. In season of birth analyses, only a day-to-day distribution, viewed without undue stress upon any calendar limits, will point up the areas of real peaks or lows in the distribution.

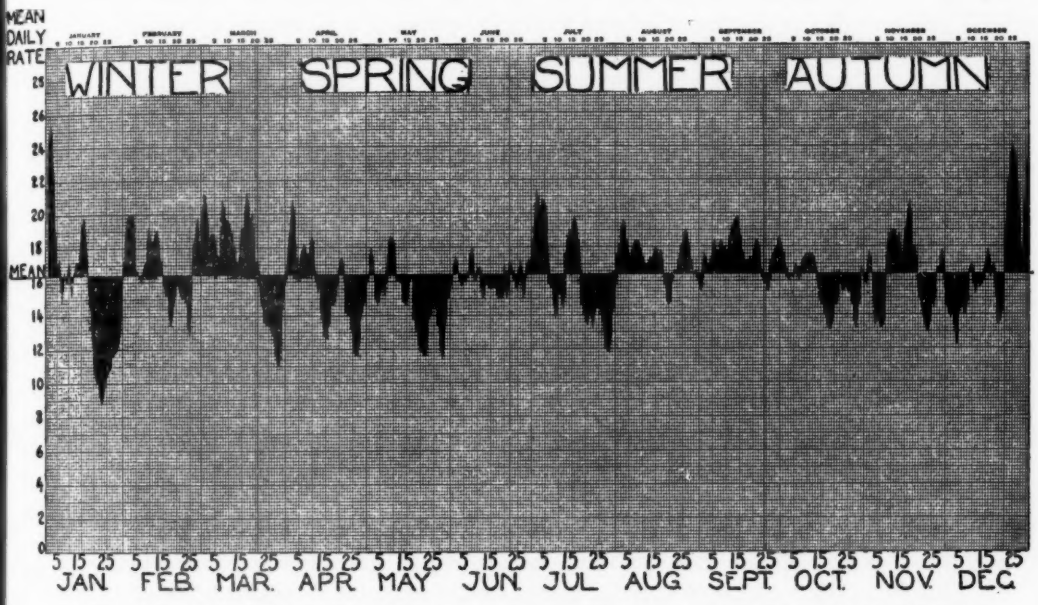

CHART A. Distribution of five-day moving average frequencies for dates of birth of 5,986 persons dying of pulmonary tuberculosis in New York City.

From our day-to-day frequency distribution a smoothed-curve graph was made by converting the actual frequencies to a five-day moving average cycle. Thus, the frequencies for the days January 1 through January 5 were totaled and divided by 5. This gave the average frequency for the middle day of the group, January 3. Next, the frequencies for the five-day group from January 2 through January 6 were added, and their average assigned to January 4. The year was considered as a closed circle, with the last two days of December averaged with the first three days of January to obtain the average for January 1, and so on. In this manner, every day of the year had an average frequency assigned to it, and we were able to obtain a curve more truly descriptive of the day-to-day trend, without the chance fluctuations of the original distribution (chart A).

Chart A was made from this five-day moving average distribution. It shows

the average daily rate for every day of the year. The mean expectancy for the entire group is 16.4. Variations are shown above and below this expected average. A glance at the chart will show that our results reported for the months and seasons are generally true. Spring remains a season of consistently below average frequencies, during which the month of May has the most protracted period of such below average frequencies. Autumn shows more variations above the mean than spring, but there are no marked peaks or low points. The graph for summer shows why August and September yielded such high means, and July did not. Evidently it is not the entire summer which is unfavorable, or tending to greater susceptibility to pulmonary tuberculosis. There is a portion in July which tends to be favorable. Going back to our original distribution, we find that the thirteen-day period from July 19 to July 31 yields a total frequency of 172, which gives a mean daily rate of 13.2. The average for the summer, exclusive of these thirteen days, rises to 17.6. There is a statistically significant difference between these means, for the critical ratio is 3.55.

Let us look at that portion of the graph describing the winter season. This showed up as the least favorable season of the year in our season analysis. The variations above and below the expected mean are remarkable. Actually, the highest concentration of frequencies and the lowest concentration occur within this period. Obviously, an analysis by areas is justified. First, let us compare the highest peak with the very low area following it. From December 22 through January 4, a period of fourteen days, the mean daily frequency rises to 21.6, the highest obtained for any time of the year. Almost immediately following it, is the fourteen-day period from January 18 through January 31. The mean daily frequency for this period is 11.0, with a standard deviation of only 2.6, which describes the consistency of the frequencies in this area. The actual frequencies for these fourteen days are: 14, 10, 12, 10, 9, 10, 9, 6, 14, 13, 12, 13, 7, 15. Note that none of the frequencies even approaches the mean expectancy of 16.4. The peak period shows more marked variations, as the standard deviation would imply. They are given here for comparative purposes. Beginning with December 22 we have: 12, 20, 22, 35, 22, 21, 18, 11, 15, 25, 40, 26, 16, 20. The highest daily frequencies for the year occur within this area.

It is of interest that the area, January 18 through January 31, is just six months removed from the other period of notably low means, July 19 to July 31. An astronomical fact may be worthy of note in this connection. The distance of the earth from the sun is least in January and greatest in July. These are times of lowest and peak temperatures, also.

There is one other area during the winter which shows a consistent high frequency rate, from about March 1 to 20. The mean for this period is 18.9 ± 5.6, which exceeds the average of the entire winter (17.3) by 1.6.

Further notes: I was curious to see whether the general pattern of peaks and lows remained if the entire group was split into categories by sex and color. Chart B was constructed to illustrate the results of these more detailed distributions.

The chart was constructed in the same manner as chart A. The day-to-day frequencies for each category were obtained. Then five-day averages were

assigned to the middle day of each five-day unit. The chart, therefore, represents a five-day moving average distribution of frequencies for each of the four categories: male-colored, female-colored, male-white, female-white.

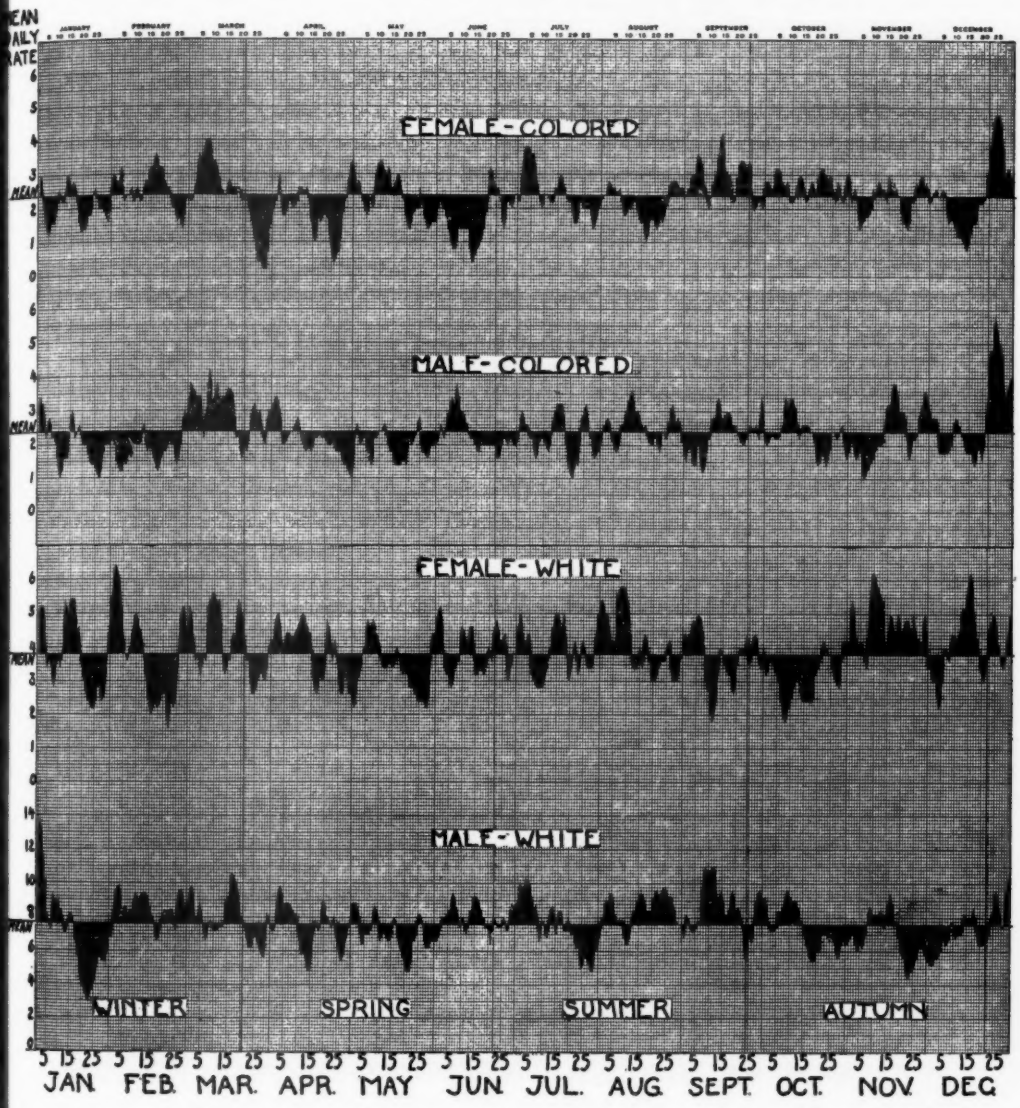

CHART B. Distribution of five-day moving average frequencies for dates of birth of persons dying of pulmonary tuberculosis in New York City, by sex and color.

Since, by breaking up the total group our total number of cases for each category became smaller, elaborate statistical calculations seemed unwarranted, as they could only be accepted as tentative or no more than indicative of a trend. Chart B will serve to demonstrate the facts. The differences in range for the

daily average rates from group to group are directly dependent on the differences in the sizes of the groups. The male-white group was the largest, representing 47.2 per cent of the total of all whites plus all colored combined; next came the female-whites, 23.9 per cent; then the male-colored, 14.5 per cent; and last, the female-colored, 14.4 per cent. It will be noted that those areas which were significantly high in the total group (chart A) remain above average in each of the subgroups shown in chart B. The same consistency is to be seen for the areas of low frequency. Naturally, there are many fluctuations due to the reduced sizes of the groups, and therefore the reliability of the variations is lessened; yet, the consistency of the significant areas is a factor to be considered. Evidently, the seasonal fluctuations remain similar for the sexes and for the two major racial groups represented, the whites and the colored.

CONCLUSIONS

Careful study of the results reported here indicates that there does exist a relationship between date of birth and the likelihood of dying from pulmonary tuberculosis.

In terms of months, May shows the lowest rate of susceptibility, while August and September show the highest.

In terms of season, those of milder temperatures, spring and fall, show lower rates than those of extreme temperatures, summer and winter. Spring is the season of least susceptibility.

An analysis by smaller areas or periods of the year reveals exceptions within these major generalizations.

The lowest mean daily rate of birth for those dying of pulmonary tuberculosis was in late January, from about the 18th to the 31st, in the midst of a season of high rates. A corresponding period occurs in the midst of summer, which also has a generally high rate. The low period occurs from July 19 to July 31, exactly six months after the winter period.

The area of peak daily mean rates occurs from December 22 through January 4; and early March, from 1 to 20, also shows a high rate.

The variations observed recur with consistency even when the group is analyzed according to sex and color.

These area delimitations must not be interpreted literally. They are guideposts for periods of the year, and most likely the days immediately preceding or following them might be included, given another distribution. The concentrations of frequencies, however, at these approximate times, can be expected to repeat themselves statistically, as all are statistically significant observations.

CONCLUSIONES

El cuidadoso estudio de los resultados comunicados indica que existe cierta relación entre la fecha del nacimiento y las probabilidades de fallecer de tuberculosis pulmonar.

En términos de meses, mayo muestra la menor susceptibilidad, en tanto que agosto y septiembre revelan la mayor.

En cuanto a estaciones, las de temperaturas más moderadas, primavera y otoño, muestran coeficientes más bajos que las de temperaturas extremadas, verano e invierno. La primavera es la estación de menor susceptibilidad.

Un análisis circunscrito a zonas o períodos del año más limitados revela excepciones que se apartan de las grandes generalizaciones expuestas.

Para los que mueren de tuberculosis pulmonar el menor coeficiente diario medio de natalidad fué hacia fines de enero, del 18 al 31, a mediados de una estación de coeficientes altos. Obsérvase un fenómeno correspondiente a mediados del verano, que también tiene un coeficiente en general alto, o sea del 19 al 31 de julio, precisamente seis meses después del período invernal.

El período de coeficientes diarios máximos medios es del 22 de diciembre al 4 de enero; y la primera parte de marzo, del 1° al 20, también muestra coeficientes altos.

Las variaciones observadas recurren con constancia, aun analizando el grupo conforme a sexo y color.

No hay que interpretar al pie de la letra estas demarcaciones cronológicas. Son más bien postes que señalan épocas del año, en las que, con otra distribución, habría probablemente que incluir los días inmediatamente anteriores o posteriores. Sin embargo, cabe esperar la repetición estadística de esas concentraciones de frecuencias, a dichas fechas aproximadas, pues todas esas observaciones revisten importancia estadística.

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CARCINOMA SIMULATING PULMONARY TUBERCULOSIS[1]

Differential Diagnosis in the Presymptomatic Stage in Two Cases

LOUIS E. SILTZBACH

A wide segment of our adult male population has recently been surveyed by mass chest X-ray methods at induction into the Armed Forces. Through this procedure, unsuspected abnormalities of the lungs, mediastinum, thoracic cage and heart have been disclosed, many of them in the presymptomatic stage. The most fruitful result of these surveys has been the discovery of early and consequently more remediable pulmonary tuberculosis. Since the age of the group examined was below 40 years, it is understandable that carcinoma of the lung has been but rarely encountered. However, similar surveys are being increasingly made among industrial groups which include many persons above the age of 40 years, and one of the lesions being brought to light is asymptomatic circumscribed carcinoma of the lung.

The roentgen appearance of a circumscribed pulmonary carcinoma may be simulated by a solitary noncavitary tuberculous focus. Indeed, in the reports of any large series of pneumonectomies for bronchial carcinoma, there will be instances in which lungs containing an isolated, large, tuberculous nodule have been excised under the impression that they contained a neoplasm.

In the 2 cases reported here, the situation was reversed. These patients were treated for pulmonary tuberculosis for periods of seven and sixteen months, respectively, before the neoplastic nature of the lesions was recognized.

CASE REPORTS

Case 1: A 61 year old man had a roentgen film of his chest made in an industrial survey in December, 1943. He was told that he had a tuberculous lesion in the right upper lobe and was referred to his family physician. After further X-ray study, the physician agreed with this diagnosis. The film showed a faint amorphous density, about 2 cm. in diameter, in the subapical portion of the right upper lobe (figure 1A). The mesial and lower borders of the density appeared somewhat rounded and it faded off laterally into several streaks. A lateral film showed that the lesion was located in the posterior portion of the lobe, a predilection site for early tuberculosis. The patient had kept a chest film made routinely three years previously and this disclosed normal lung fields.

He was sent to a tuberculosis institution where the gastric contents were searched for tubercle bacilli by means of smears, cultures and guinea pig inoculations. All yielded negative results. Since he remained free of symptoms and the lesion appeared unchanged, he was discharged as arrested after an eight weeks' stay. He returned to work, continued to feel well and visited his physician for another chest film four months later. The lesion now appeared denser and had grown to 3 cm. in diameter. He was nevertheless allowed to continue his work. One month later he felt a dull pain in the right scapular region and visited another physician. A chest film showed further increase in the size and density of the lesion. The borders were sharper and the diameter measured about 4 cm. (figure 1B).

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The fingers showed early clubbing and it was thought that the patient had a bronchial carcinoma. He was admitted to The Mount Sinai Hospital on June 28, 1944, seven months after the lesion had been discovered. There was no weight loss during this period.

On admission the patient was found to be well nourished. Physical examination showed no abnormality aside from slight clubbing of the fingers. Tubercle bacilli could not be found in the sputum or gastric contents and bronchoscopy did not reveal any abnormal findings. Roentgen study of the dorsal spine and ribs revealed no abnormality and an electroencephalogram disclosed a normal pattern.

The chest was explored on July 12, 1944. A walnut-sized mass was palpated in the posterior portion of the right upper lobe. This lobe and the right middle lobe, which adhered firmly, were extirpated. Although the regional nodes did not appear to be involved grossly, several were removed for study.

On section, the tumor was found to be sharply circumscribed. Microscopically, it proved to be an epidermoid carcinoma. The lymph nodes showed no tumor cells. There was no evidence of a tuberculous lesion. The postoperative course was complicated by an empyema which was drained. The patient was discharged with a small sinus after a ten weeks' stay. The sinus closed in March, 1945. The patient works full-time and has no symptoms aside from mild dyspnea with exertion. There has been no evidence of recurrence of the neoplasm for two years following the operation.

Circumstances leading to the correct diagnosis in the second case parallel those of the first, with the exception that this patient was considered tuberculous for sixteen months before admission to the hospital.

Case 2: A woman of 43 had an industrial chest survey film made in April, 1944. A right upper lobe lesion was found and, after study in a tuberculosis clinic, the patient was told that she had arrested pulmonary tuberculosis. There were no pulmonary symptoms. The lesion was faint, appeared oval shaped and measured about 2 cm. in diameter (figure 2A). Its outer border was hazy and several streaks extended from it peripherally. The sputum and gastric lavage specimens were negative for tubercle bacilli on smear and culture and, since the patient had no complaints, she was allowed to return to work. Two more chest films made at intervals of one month showed no change in the size of the lesion but there was a slight increase in its density.

In October, 1944, six months after the discovery of the lesion, a film revealed a few moth-eaten areas of lesser density within the shadow, but it had still not changed in size (figure 2B). Three months later, the shadow was larger and stood out more sharply from the surrounding lung parenchyma. In spite of these changes, the woman was allowed to continue with her work. In June, 1945, the shadow exhibited considerable expansion; it now measured 4 cm. in diameter. Her physicians decided that she now had active tuberculosis and sanatorium care was recommended. While waiting for admission she consulted another physician who thought that her film series indicated the presence of a slow-growing circumscribed neoplasm. He referred her to The Mount Sinai Hospital and she was admitted on August 20, 1945, sixteen months after the pulmonary lesion had been discovered. There had been no weight loss throughout the period.

On admission, the patient had no complaints and she appeared well nourished. Physical examination disclosed no abnormalities. The blood pressure was 142/60. An electrocardiographic tracing showed a normal pattern. The gastric contents revealed no tubercle bacilli. A Mantoux test was positive. An intravenous pyelogram, a gastrointestinal X-ray series and an electroencephalogram were all negative. A recent instance

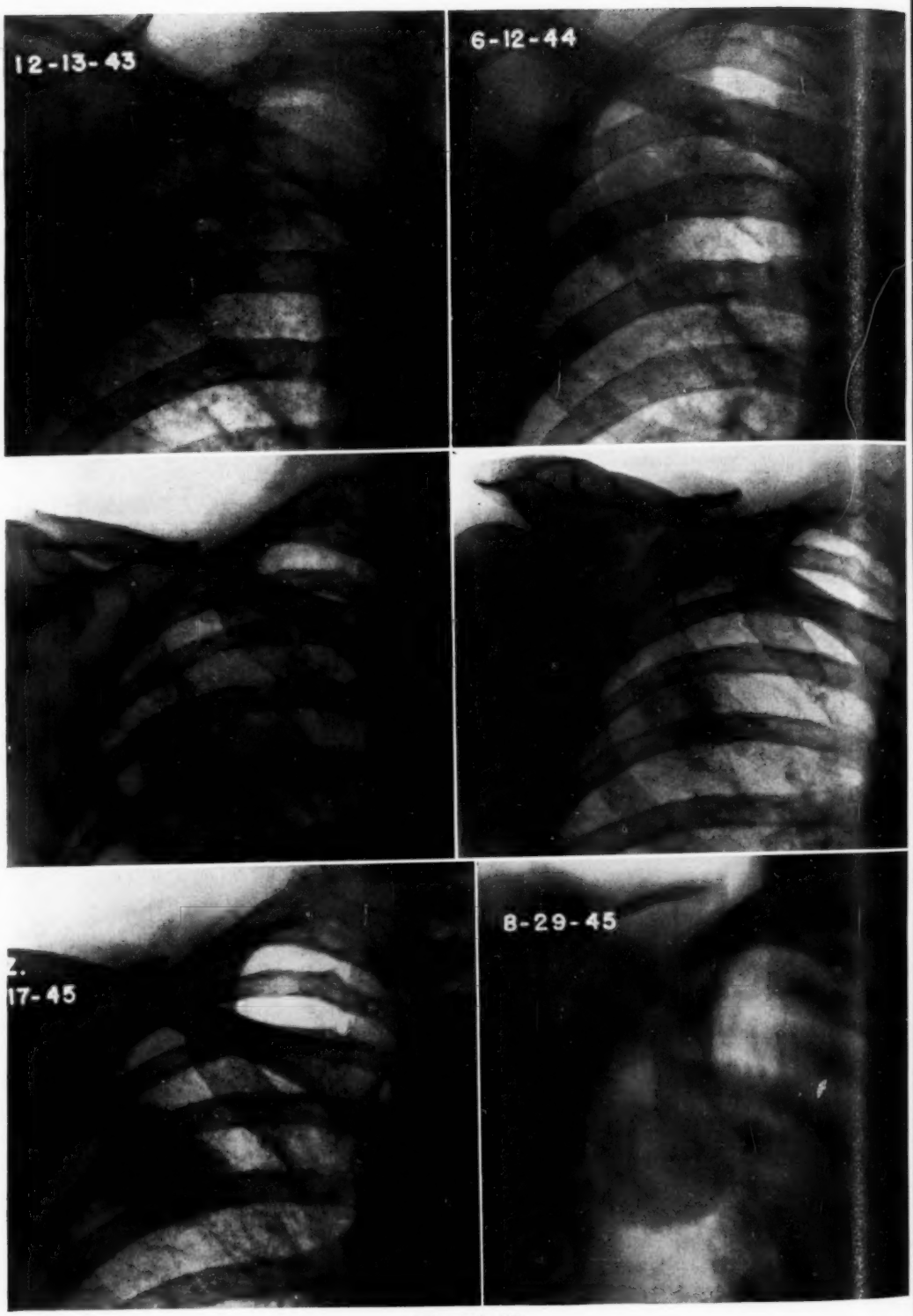

FIG. 1A–2D

of a solitary pulmonary metastasis from a hypernephroma has prompted us to add intravenous pyelography to our preoperative investigation. No other primary site could be found nor was there any evidence of distant metastatic lesions. A posterior-anterior view of the chest showed the dense oval shadow in the right upper lobe (figure 2C). The lateral chest film showed the lesion to be located in the posterior portion of the upper lobe and sectional radiography disclosed several irregular areas of decreased density within it (figure 2D).

The chest was explored on August 29, 1945. As the pleural cavity was entered the pulse became imperceptible and no blood pressure readings could be obtained. The operation was discontinued and the chest was closed. The patient responded to anti-shock therapy within a few hours. Neurological examination and electrocardiography disclosed no abnormalities. There were no sequelae and the patient was allowed out of bed on the fourth day. After two weeks she was again operated upon. A transfusion was started before the pleura was opened. Despite this, there was the same shock-like reaction with a marked fall in blood pressure. Small doses of neosynephrin intravenously brought the blood pressure back to nearly normal levels and a partial lobectomy of the portion of the lobe containing the tumor was performed. No involvement of the lymph nodes, pleura or chest wall was noted.

Grossly, the specimen showed a well circumscribed oval neoplasm; in its centre were several small areas of necrosis; it was an adenocarcinoma. A small bronchopulmonary lymph node showed no tumor cells. No tuberculous lesions could be found. A few hours after operation, the patient again lapsed into a state of shock which resisted all forms of therapy. She died sixteen hours after the operation. Permission for postmortem examination could not be obtained.

In the absence of clinical evidence of air embolism after either operation, one may speculate on the possibility of the occurrence in this instance of true "pleural shock." Anesthetists have reported such phenomena during thoracic operations and have successfully combated the vasomotor collapse by vagal block with procaine.

COMMENT

These 2 cases point up some of the difficulties in differentiating between a slow-growing circumscribed neoplasm of the lung and a solitary tuberculous focus,

FIG. 1A. (Upper left) Case 1. Chest film, 12/13/43, taken soon after an industrial survey disclosed a lesion in the right upper lobe which was considered to be tuberculous. The lesion is veil-like with a rounded mesial border and lateral streaking.

FIG. 1B. (Upper right) Case 1. Chest film, 6/12/44. Seven months later, the lesion is denser and larger. It stands out more clearly from the surrounding lung parenchyma.

FIG. 2A. (Centre left) Case 2. Chest film, 5/15/44, taken soon after an industrial survey disclosed a lesion in the right upper lobe. The shadow is faint and has a somewhat rounded mesial border. The lateral aspects of the density are streaked. (Reproduced from paper film.)

FIG. 2B. (Centre right) Case 2. Chest film, 10/16/44. Five months later, there is no significant increase in the size of the right upper lobe lesion but it is denser. (Reproduced from paper film.)

FIG. 2C. (Lower left) Case 2. Chest film, 8/17/45. Sixteen months after discovery the lesion has increased to about 4 cm. in diameter. It is oval-shaped, denser and stands out sharply.

FIG. 2D. (Lower right) Case 2. Sectional radiogram, 8/29/45. An area of lesser density within the lesion just lateral to the first rib indicates central necrosis of the mass.

particularly when the lesion is situated in the upper lobes. A proper evaluation of the alterations in the appearance of the lesion on successive films was crucial in both these cases, since neither of the patients had any symptoms for the many months of observation prior to surgery.

It must be recognized that circumscribed bronchial carcinoma may be silent for a prolonged period and, in this respect, behaves like some cases of early pulmonary tuberculosis.

The progression of the lesions on the roentgen film in these 2 cases may be summed up as follows: Initially, both lesions measured about 2 cm. and had a veil-like, somewhat amorphous appearance, but on close inspection it could be seen that the mesial borders were rounded whereas the lateral borders faded out and were streaky. These streaked shadows probably represented small foci of atelectasis arising either from obliteration of small bronchial lumina by the neoplasm or from pressure exerted upon the lumen by the expanding extramural mass. Some of the veiled shadow may also have represented atelectatic lung tissue.

Later, the shadow became denser and more sharply demarcated from the surrounding lung parenchyma and it then represented the neoplasm itself. In the second case, the increase in density and the sharpening of its circumscription were the only changes noted during the first six months.

An increase in its size occurred only later. The expansion was more or less concentric with the rounded contour of the mass maintained. As such neoplasms grow larger, they may occasionally become lobulated in outline.

Another distinguishing roentgen feature in the second case was central necrosis of the neoplasm, which was suggested by the presence of several small irregular areas of lesser density within the solid shadow. These areas were best demonstrated by sectional radiography.

Should such areas be visible within the mass on the initial film and should the sputum be persistently free of tubercle bacilli, such a lesion must be presumed to be neoplastic and exploratory operation is warranted.

The combination of an increase in density and the concentric expansion of a circular or oval nodule should lead one away from a diagnosis of pulmonary tuberculosis. On the other hand, the presence of multiple areas of calcification within the shadow—sometimes only demonstrable with sectional radiography—favors the diagnosis of an ancient tuberculous focus. If there are other tuberculous lesions within the lung fields, this diagnosis is considerably reinforced. Although a fresh tuberculous infiltration may sometimes assume a circular or oval contour, its spread is not likely to be concentric but rather takes the form of acino-nodular or bronchopneumonic lesions in the neighboring or distant segments of the lung. In the course of healing without spread, such round or oval foci grow smaller as their density increases.

The streaked shadows described in these 2 cases extended from the lateral border of the density and radiated peripherally. When streaking exists with a similar tuberculous focus, the strands tend to arise from the mesial border and extend in the direction of the hilum. This mesial streaking is noted particularly in instances of a solid shadow arising from a blocked tuberculous cavity.

Circumscribed neoplasms sometimes exhibit necrosis which may progress to gross cavitation. In general, the walls of such cavities are thicker and are more likely to show irregular scalloping of the inner margin than do tuberculous cavities. The presence or absence of tubercle bacilli in the sputum or in the gastric contents is an all-important diagnostic criterion in such instances.

Other diagnostic measures unfortunately are seldom helpful. A negative tuberculin test is not too common in patients over 40, particularly in urban areas. Even when a negative test is present, it does not completely exclude tuberculosis. Nor can much information be gained from bronchoscopy, since the location of the lesion most often places it beyond the view of the bronchoscopist. A previously normal chest film may be of help, since the appearance of a neoplasm in patients above 40 is probably more common than the occurrence of a fresh solitary tuberculous focus. However, tuberculous lesions can first make their appearance in this age group, particularly if the patient is a diabetic. The presence of enlarged lymph nodes at the lung root in the early course of a circumscribed neoplasm is uncommon.

If symptoms and signs do appear in circumscribed carcinoma, the early ones are often chest pain and clubbing of the fingers. Occasionally the first symptom is hemoptysis. Aspiration biopsy is difficult to perform because the lesions are small and, in the instances reported here, they were covered by the scapula. In general, this procedure is not practiced where surgical intervention is contemplated, since there is some hazard of spreading the malignant tissue to the pleura and along the needle track.

One cannot afford to wait long for expansion and changes in density of the lesion since blood-borne metastasis and lymphatic extension are ever-present threats. The decision to explore the chest for a biopsy should be made in weeks rather than in months as was the case with the 2 patients reported here. When the above-cited diagnostic resources have been exhausted, an exploratory operation becomes advisable. There is in this procedure the danger of empyema should the lesion prove tuberculous but this is probably quite small and is considerably outweighed by the chance of saving life when the lesion is carcinoma.

At the present time, physicians are aware that pulmonary tuberculosis produces few symptoms and signs at its onset and that the diagnosis must be made in this stage if the chances of recovery are to be kept at their maximum. This is no less true of the circumscribed variety of bronchial carcinoma. Mass surveys and routine chest roentgenography in hospitals and in the physician's office are rapidly becoming the important method by which operable pulmonary cancers are discovered. The 2 cases reported here were mistaken for pulmonary tuberculosis for seven and sixteen months, respectively, before they were admitted to a hospital for surgery. In this communication, the causes for the delay in diagnosis were examined.

SUMMARY

1. Industrial mass surveys which include many persons above 40 years of age are bringing to light silent circumscribed lung carcinomata.

2. Two patients with such neoplasms, the shadows of which were first disclosed in survey films, were treated for pulmonary tuberculosis seven and sixteen months, respectively, before the nature of the lesion was recognized.

3. The differential diagnosis between a solitary non-cavitary tuberculous focus and a slow-growing circumscribed carcinoma in patients over 40 years of age—particularly when the lesion is situated in the upper lobes—is discussed. The roentgenographic characteristics of such neoplastic and tuberculous lesions are presented.

4. Early exploratory thoracotomy is suggested when the diagnosis is equivocal, since this procedure may be life-saving if the lesion is carcinoma.

SUMARIO

1. Las encuestas colectivas en la industria que comprenden muchas personas de más de 40 años van poniendo de manifiesto la existencia de carcinomas pulmonares circunscritos y silenciosos.

2. Antes de reconocerse la naturaleza de la lesión, a dos enfermos con neoplasias de dicha naturaleza, cuyas sombras revelaron por primera vez las películas de la encuesta, se las trató por tuberculosis pulmonar por espacio de siete y diecicéis meses, respectivamente.

3. Discútese el diagnóstico diferencial entre un foco tuberculoso solitario sin cavernas y un carcinoma circunscrito de desarrollo lento en enfermos de más de 40 años—en particular cuando la lesión radica en los lóbulos superiores. Expónense las características radiográficas de dichas lesiones neoplásicas y tuberculosas.

4. Propónese la ejecución de una toracotomía exploradora temprana cuando el diagnóstico es dudoso, pues puede salvar la vida si se trata de carcinoma.

TUBERCULIN TESTING IN STUDENT NURSES[1]

MAURICE N. SHOOR[2]

Many studies have been done in which persons have been observed for tuberculin conversions. Most of these have been in work with medical students and student nurses, and were concerned with the early discovery of new cases of active tuberculosis. Tuberculin tests on admission and repeated tests on the negative reactors every four to six months were followed with X-ray films at frequent intervals after a positive tuberculin test occurred.

It has been demonstrated in recent years that the number of reactors on admission to medical schools or nursing schools has been steadily decreasing. It has also been shown that by careful techniques on the wards a smaller percentage of conversions and fewer cases of clinical tuberculosis develop. Keller and Kampmeier (8) showed an increase from 54 per cent tuberculin-positive nurses on admission to only 58 per cent positive on graduation, among 198 student nurses at Vanderbilt University. However, most studies show that, by the time they graduate, almost all have become positive to tuberculin (Ornstein and Myerowitz (14); Meyers *et al.* (12); Israel *et al.* (6); Riggins and Amberson (15); Geer (3); and Badger and Spink (1)).

These authors have also demonstrated that, of the total number of persons who become positive to tuberculin, only a very few develop an active parenchymal lesion. Hence the great majority of these nurses seem to handle their contact very well.

Myers (13), however, feels that all tuberculin-reactors must be considered as having a phase of tuberculosis and should be carefully watched. Ornstein and Myerowitz (14) believe that, of all people who become tuberculin-positive, the majority goes on to complete healing. Statistical study shows that actually very few go on to develop active pulmonary tuberculosis: Geer, 1.6 per cent; Amberson and Riggins, 1.4 per cent; Badger and Spink, 1.7 per cent.

The problem of whether a lesion is of primary or reinfection type frequently arises in these studies. Recent works seem to favor the theory that such a differentiation is not often possible roentgenologically. It is thought by some (Sweany (18)), that the reaction to tubercle bacilli of most adults varies from that of the child or adolescent, and hence the reactions will vary in appearance. Israel and Hetherington (6) demonstrated only one case of hilar adenopathy in 62 student nurses who developed active tuberculosis following tuberculin conversion. Sweany (18) also pointed out that primary infection in children is not always benign and occasionally goes on to progressive and fatal disease. Such a reaction in an adult may also be primary and doesn't rule out a first infection.

Israel and Long (7) came to the conclusion that a lesion can be called primary only if the person concerned has been closely followed with tuberculin tests, and

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a direct relationship has been established between the onset of the disease and tuberculin conversion. They also found that most cases of active disease appeared a year or more after tuberculin conversion and were probably not primary in type.

The problem is far from being settled, and we must constantly revise our way of thinking about this. The N.T.A. Diagnostic Standards have changed several times and undoubtedly will again have to revise its definition of primary and reinfection type disease.

Few of these studies have been concerned with X-ray changes which might be coincident with the tuberculin conversion. Shipman and Davis (16) in a study of student nurses could find no such correlation. Myers (13) speaks of a pneumonic area appearing around the tuberculous focus soon after the tissues become sensitized. These, however, last for months, or a year or more and then gradually disappear.

It is known and accepted that, when tuberculin conversion occurs, there must also be a site of infection somewhere in the body. The lung being the organ most often affected, it is also the most probable site for the initial infection.

It seems that if looked for at the proper time, this transient infection should be identifiable by X-ray examination, at least in some cases.

In January, 1941 a Federal Grant Class of 100 student nurses was admitted at the Los Angeles General Hospital. These were high school graduates with an average age of 18 to 19 years. A Mantoux skin test with 0.01 mg. of OT was performed on each member of the group on admission. Only 21 girls had positive skin tests and 79 were negative.

This presented an opportunity to study a number of factors relative to their probable contact with tuberculosis, such as the number of conversions, the rate of conversion, associated symptoms and possible X-ray changes at the time of conversion. The girls were carefully observed for possible early active lesions.

It was decided to perform Mantoux tests monthly on all the negative reactors, using 0.01 mg. OT, and to read the tests after forty-eight hours. Following each conversion, chest films were to be taken immediately, and monthly for four months, and another film at six months, and then one at one year following conversion. A yearly film was to be taken and a final film at the termination of training.

In order to ascertain whether there were any associated clinical manifestations, all reactors were asked to report any unusual symptoms which they might note. These were colds, aches, pains, lassitudes etc. Daily afternoon temperatures were to be taken for a month following conversion. The study was continued for two years with monthly Mantoux tests. Final films were taken of all students who developed a positive tuberculin test, at the end of three years.

During the two-year period, many students dropped out and only 55 students graduated. None dropped out for any reason connected with tuberculosis. There were other reasons of health, incompatability and inability to carry on the work etc.

RESULTS

There were 12 conversions from negative to positive tuberculin allergy. This is 15 per cent of the original group, or 27 per cent of the final remaining group. The time of conversion was as follows:

2—1st month
1—2nd month
1—4th month
1—6th month
1—9th month
1—11th month
1—13th month
4—last nine months

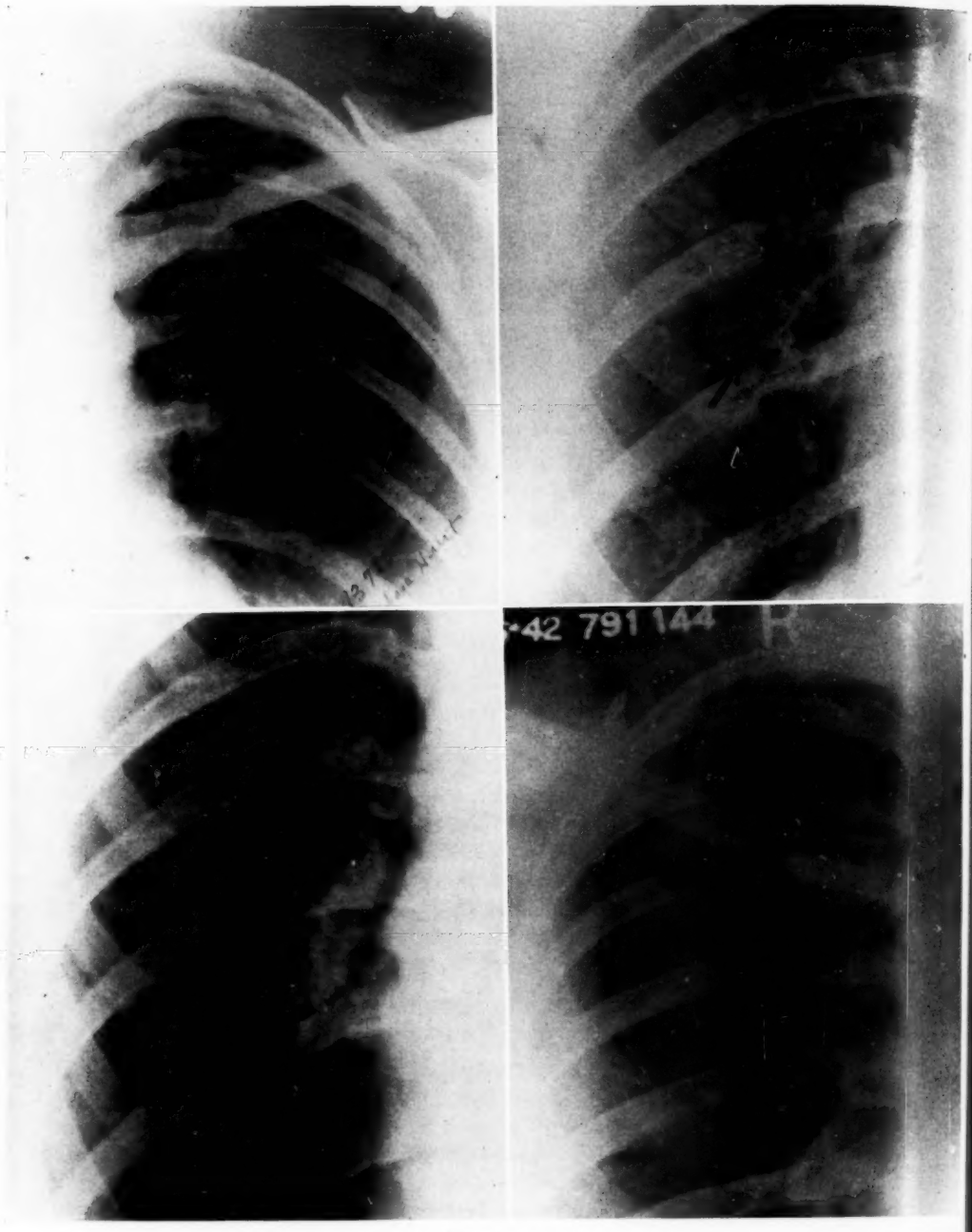
It was noted that none of the girls had any evidence of upset preceding, coincident with, or following the conversion—with one exception. The latter will be described in more detail later, as the first case. There were no elevations in the temperature curves of the 11 girls who checked them for one month following their conversions, and there were no reports of aches, pains or lassitude. The only clinical evidence these girls had of a change was the positive Mantoux test on their forearm.

Case 1: B. H. She was tuberculin-negative on admission in January, 1942 and monthly till November, 1943. Her tuberculin test was positive in December but she was admitted to the hospital between the application of the test and the time of reading with the diagnosis of "flu."

Unfortunately no X-ray film was taken at the time and it was not reported to me that she had become positive. In January, 1944 her tuberculin reaction was read as positive and then the previous data were elicited. A film taken January 15, 1944 showed a soft irregular patch of infiltration in the left apex, minimal in amount (figure 1). She was put to bed and did very well. Her films of May 25, 1944 showed considerable regression and those of August 24, 1944 showed the left apex clear. She spent about a year in bed and, after a period of time at home, returned to complete her nursing course and is now completely well.

Case 2: S. P. She was tuberculin-negative on January 2, 1942 and her X-ray film was clear at this time. Tuberculin tests remained negative until January, 1943 when she had a positive skin test. An X-ray film of the chest on January 8, 1943 revealed a thickening of the vascular pattern in the right lower parahilar region (figure 2); this remained present and films in April (figure 3) and May showed the same lesion but more sharply outlined. By December 10, 1943 there had been much clearing, leaving a faint rounded patch in the third anterior intercostal space. By June 3, 1944 the area was clear again. This girl had no symptoms of any kind and continued her nursing course with no distress and no apparent ill effects.

Case 3: R. P. Her X-ray film was clear on admission and she was tuberculin-negative on monthly tests until April, 1942. A roentgenogram of the chest on April 10, 1942 showed a slight haze in the first anterior interspace in the mid-clavicular line; this was of doubtful nature. It persisted until July, 1942 (figure 4) when this area showed a more definite



FIGS. 1–4

FIG. 1. (Upper left) B. H. January 15, 1944. At time of conversion; minimal lesion in left apex.

FIG. 2. (Upper right) S. P. January 8, 1943. At time of conversion; lesion in right hilar area.

FIG. 3. (Lower left) S. P. April, 1943. Lesion the same.

FIG. 4. (Lower right) R. P. July, 1942. Haze in right first intercostal space, between the fifth and sixth posterior ribs.

patch described as a hazy exaggeration of the reticular pattern. By September 1, 1942, the area was clear again. This girl had no symptoms or signs of any kind and continued her work uninterruptedly.

Case 4: J. D. Her X-ray film of the chest was clear on admission and monthly tuberculin tests were negative until March, 1942. A film taken April 10 showed an indefinite cloudy appearance in the left parahilar region which was not present before. Film of May 15, 1942 was clear. This girl had no symptoms or signs of any type.

Case 5: M. H. Her chest roentgenogram was clear on admission and her tuberculin tests were negative till April, 1942. Her X-ray film in April was clear. The film of May 15, 1942, showed a small area with accentuation of the vascular shadows in the lateral portion of the left fourth intercostal space. Her film in September was clear again.

DISCUSSION

Certainly no conclusions can be drawn from so few cases. But I believe they are interesting, because they possibly show a phase of the disease not usually seen.

The first girl presented the picture of a typical minimal tuberculosis of the so-called reinfection type. But two months before the discovery of this lesion, her tuberculin test was negative. It is possible that this was actually her reaction to her primary infection. No hilar lymph node component could be seen. If this actually was a reinfection-type disease, this girl must have gone very rapidly through her primary infection and then developed another lesion in the apex. It seems more likely to me that this represented her primary infection.

The second and third cases present transient foci of fairly definite appearance which manifested themselves shortly after tuberculin conversion. They did not incapacitate the girls in any way and gradually disappeared. Here again there were no hilar adenopathies demonstrable on the X-ray films. These foci might very well represent the primary tuberculous infection in the young adult clearing in the great majority of instances, some slowly and some more rapidly.

The last 2 cases may show the very rapid clearing of a primary infection. They each presented a questionable focus on one film only, with subsequent films clear; the girls remained well at all times. Here also, no evidence of hilar adenopathy was found.

These last 4 cases may possibly represent the type of reaction which occurs in people who become positive to tuberculin after contact with tubercle bacilli, but who never have any symptoms or signs of illness. It seems likely that a more extensive study might bring more such lesions to light and tell us more about them.

It is also of interest to note the small number of conversions, 27 per cent of the final group or 15 per cent of the original group. There certainly was contact with tuberculosis in a large general hospital, and we know that one-third to one-fourth of the patients in the Tuberculosis Unit of the General Hospital come from the general wards. It may be that this group of girls being tuberculosis conscious, due to this study, was more careful in its contacts with coughing

patients. It should be mentioned that none of the students work on the Tuberculosis Service with a negative Mantoux test at the Los Angeles General Hospital. They do work on the general medical and surgical wards and the various medical and surgical specialty wards. Many patients on these wards are emergency admissions and obviously cannot be filtered for tuberculosis when admitted.

It was interesting to note that there was no time when a large number of conversions occurred. They just came, one every so often throughout the two-year period of study.

It has been suggested, on occasion, that frequent applications of tuberculin in themselves might sensitize an individual. It seems apparent that, were this so, a much larger percentage of cases would have become positive by the end of the second year, and that such sensitization does not occur as a general rule.

SUMMARY

1. Serial tuberculin tests were done on the negative reactors of a class of 100 student nurses.

2. Of the original group of negative reactors 15 per cent developed tuberculin sensitivity during the two-year period of the study.

3. Only one student showed clinical symptoms at the time of conversion; she rapidly developed an active minimal lesion.

4. Five students had some X-ray evidence of infection coincident with or shortly after conversion of their tuberculin tests.

5. In this series of observations, no evidence was found that sensitization was caused by repeated tuberculin tests.

SUMARIO

1. En las reactoras negativas que formaban parte de una clase compuesta de 100 estudiantes de enfermería ejecutáronse pruebas a la tuberculina seriadas.

2. Del grupo primitivo de reactoras negativas, 15 por ciento manifestaron sensibilidad a la tuberculina durante el período de dos años comprendido en el estudio.

3. Una sola de las estudiantes reveló síntomas clínicos en la época del viraje, manifestando rápidamente una lesión mínima activa.

4. Cinco estudiantes mostraron algunos signos roentgenológicos de infección coincidente con el viraje de las pruebas a la tuberculina o poco después.

5. En esta serie de observaciones no se descubrieron pruebas de que la sensibilidad se debiera a la comprobación repetida con tuberculina.

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A METHOD OF X-RAY REPRODUCTION OF THE NEGATIVE X-RAY FILM[1]

ARTHUR REST[2] AND LEONA STROUD[3]

The roentgenogram has simplified and made apparent the diagnosis of certain diseases, the most important of which to the phthisiologist is pulmonary tuberculosis. Without serial X-ray study the management of the tuberculous patient becomes difficult. A method has been devised by us whereby a 14 x 17″ X-ray film in the positive (that is, heart shadow black) can be made of the negative X-ray film (that is, heart shadow white) that shows all the details and deviations from the normal as seen in the negative film. (See figures 1 to 3.) The positive X-ray film offers to the phthisiologist a means of obtaining a permanent record of a desired negative film that cannot be retained in his possession for future comparison or for study. From this standpoint alone the positive 14 x 17″ X-ray film replaces the small, entirely inadequate photographic paper print which has been, up to now, our usual method of reproducing an X-ray film.

TECHNIQUE

The negative 14 x 17″ X-ray film to be reproduced is placed in the cassette next to the top, or opening screen, of the cassette. An unexposed X-ray film is then placed next to the negative X-ray film, and between it and the back screen of the cassette is placed the black protecting paper that always accompanies an unexposed film. The purpose of the black protecting paper is to prevent any fluorescence emanating from the back screen of the cassette. We now have in the cassette between the opening and back screen, in the order named: the negative film to be reproduced, the unexposed film and the black protecting paper.

The following technique is then employed: 40″ distance, 100 milliamperes,

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[3] Radiographer.

FIG. 1A. (Upper left) The negative X-ray film shows a small infiltrative lesion in the first interspace peripherally of the right lung. There is a cavity at the periphery of the second rib anteriorly of the left lung with a cavity off the hilum.

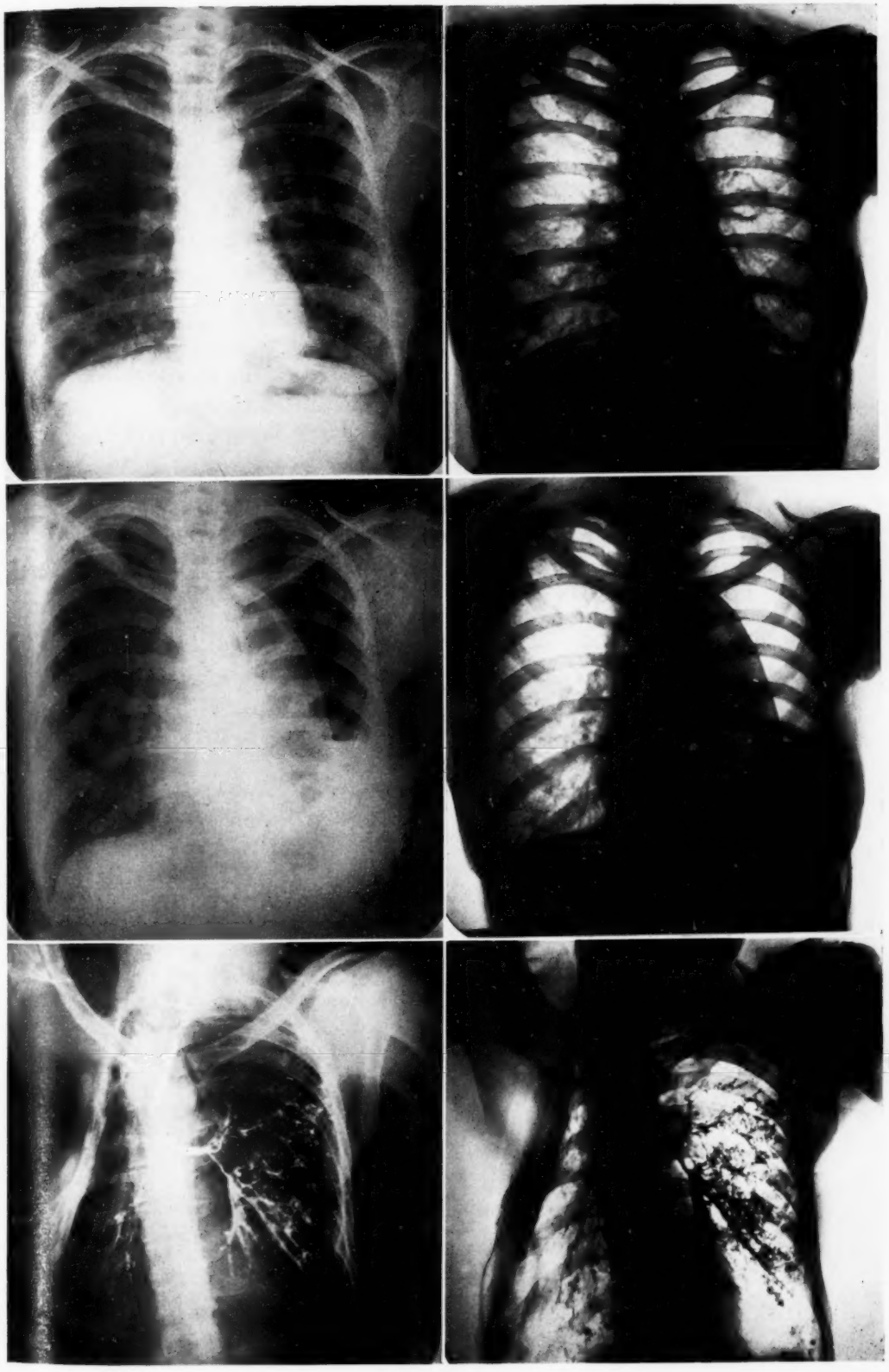
FIG. 1B. (Upper right) The positive X-ray reproduction shows these changes very distinctly.

FIG. 2A. (Centre left) In the negative X-ray film the right lung is essentially uninvolved. There is a left hydropneumothorax.

FIG. 2B. (Centre right) The positive X-ray reproduction shows the same changes.

FIG. 3A. (Lower left) The negative X-ray film shows a partial surgical collapse of the right lung with a bronchogram, particularly of the left side.

FIG. 3B. (Lower right) The positive X-ray reproduction depicts exactly what is seen on the negative film.



FIGS. 1–3

42 kilovolt peak and one half second. The X-ray film which has now become exposed is developed in the usual manner, namely five minutes at 65°F., or four minutes at 70°F.

By the same technique, a negative X-ray reproduction of the positive reproduction can further be made, if this is desired. We feel that this is not necessary as the positive X-ray film suffices in duplicating clearly the changes seen in the negative X-ray film, as demonstrated in figures 1 to 3.

SUMMARY AND CONCLUSIONS

By the Rest-Stroud technique, a 14 x 17″ positive X-ray reproduction can be made of the 14 x 17″ negative X-ray film and of any other negative X-ray film. This technique has no injurious effect on the negative film.

By the same technique a negative X-ray reproduction of the positive X-ray reproduction can further be made, if this is desired.

SUMARIO Y CONCLUSIONES

Con la técnica de Rest-Stroud puede obtenerse una reproducción radiológica positiva de 35 x 42.5 cm de las películas negativas de 35 x 42.5 cm y de cualquier otra película negativa. Esta técnica no afecta adversamente la película negativa.

Con la misma técnica, si se desea, puede hacerse además una reproducción adiológica negativa de la reproducción positiva.

AMERICAN TRUDEAU SOCIETY

Report of the California Trudeau Society

Dr. C. Gerald Scarborough, *Secretary-Treasurer*

The following is a report on the activities of the California Trudeau Society for the year ending June 1, 1946:

1. Four physicians have been given short postgraduate medical courses through the facilities of the University of California and Stanford University Hospitals, and 4 other physicians have been afforded similar training at Barlow Sanatorium in Los Angeles.

2. Eighteen County Medical Societies have been supplied with qualified speakers who have addressed meetings of these societies.

3. A committee of the Society has held meetings to arrange for the medical programs to be presented at the annual meeting of the California Trudeau Society and the California Tuberculosis and Health Association in San Francisco, April 24, 1946. An X-ray symposium for this meeting has been arranged by members of the Society.

4. Correspondence concernng affairs of the Society has been carried on by the officers and directors throughout the year.

5. A special committee concerned with the establishment of criteria to be used by Health Officers in deciding what would constitute a quarantinable case of tuberculosis under the new State law (Chapter 221, 1945) has held meetings and is actively engaged in further investigation on this subject.

6. A committee has been giving consideration to various phases of the veterans' problem as this relates to tuberculosis.

7. Members of the Society have read approximately 200,000 miniature X-ray films taken in mass X-ray surveys throughout the State.

8. One issue of *Fluorograph* was issued during the year.

9. Work on a new directory of members is being planned but has been deferred pending the return of men from the service.

Report of the Eastern Section of the American Trudeau Society

Dr. N. Stanley Lincoln, *Secretary-Treasurer*

In the fall of 1945 the members were canvassed to obtain their wishes regarding a Section meeting. Due to transportation and hotel difficulties, an acceptable place could not be found for a meeting, and upon direction by the President and Vice-President, plans for a meeting were canceled, at least until the fall of 1946.

The membership of the Section is as follows:

Number of active members	222
Number of associate members	76
Number of deaths since 1944	2
New members	0

Report of the Illinois Section

Dr. L. L. Collins, *Secretary-Treasurer*

The Fall Annual Meeting of the Illinois Trudeau Society was held at Rockford, Wednesday, February 27, 1946.

The meeting was called to order by the President, Dr. Bryan, at 2 p.m. Dr. Volini of the Municipal Tuberculosis Sanitarium in Chicago gave an excellent paper on *Ambulatory Pneumothorax*. Ambulatory pneumothorax was discussed from two points of view—first, the ambulatory patient who has had a certain amount of sanatorium care and has ambulatory pneumothorax after leaving the sanatorium, and, second, patients who received the initial and all follow-up refills outside the sanatorium. Every one present was in agreement on the first procedure, but the second procedure brought forth considerable disagreement and discussion. Every one seemed to be in total agreement, however, that circumstances would alter the choice of method. Where beds are not available and where the patient refuses sanatorium care but will accept ambulatory pneumothorax, then ambulatory pneumothorax has a definite indication. Dr. Volini reported surprisingly good results from the thousands of cases that have been treated by pneumothorax without sanatorium care.

Dr. Van Hazel gave a scholarly and most interesting dicussion on *Bronchogenic Carcinoma*. He showed several patients in whom the first symptom which caused the patient to seek medical advice was a pain in the joints. His paper brought forth considerable discussion.

Dr. William Peck of Maybury Sanatorium, Detroit, presented an interesting paper on the *Modalities of Bed-rest*. Dr. Peck stated that frequent changing of position in bed produced better drainage, muscular relaxation, mental rest and emotional stability. Dr. Peck showed several patients in whom surprisingly good results were obtained with this type of treatment.

The business meeting was called to order by the President, Dr. Bryan, at 4:45 p.m. The important business was the election of officers for the coming year. Dr. Charles K. Petter, President-Elect, was advanced to the Presidency; Dr. D. F. Loewen was elected President-Elect of the Society; Dr. Bulley, Vice-President; Dr. Collins, Secretary-Treasurer. Dr. Eugene T. McEnery was elected a member of the Executive Committee; and Dr. W. J. Bryan became a member of the Executive Committee by virtue of being the retiring president.

There were 77 physicians present at this meeting. The practicing physicians of Winnebago and the surrounding counties had been invited to attend. Dr. Coon and Dr. Gale of Wisconsin were out-of-state visitors. Both took an active part in the discussion of various papers.

A dinner meeting was held at 6:30 p.m. at the Faust Hotel. A paper prepared by Dr. Herbert R. Edwards was read by the Secretary of the Trudeau Society. This paper was received so enthusiastically that the local State Association has been requested to reprint it in their monthly paper *Contact*. We regretted that Dr. Edwards could not have been present to enjoy the enthusiasm and interest with which his paper was received.

Dr. Volini, Dr. Van Hazel and Dr. Peck addressed the meeting without written manuscripts.

Report of the Indiana Trudeau Society

M. A. Auerbach, *Executive Secretary*

There have been no meetings of the Indiana Trudeau Society during the year 1945. The only committee activity was that of an Advisory Committee to Assist in Improving Sanatorium Standards, which made a visit during the year to two sanatoria in the State.

The Indiana Trudeau Society held its annual meeting on May 8, 1946.

During the business session there was a discussion promoted by the sanatorium men regarding accounting. The President was authorized to appoint a committee to meet with the State Board of Accounts relative to devising a common plan of bookkeeping for all sanatoria in the State.

The following officers were elected: President, M. R. Lohman, M.D., Fort Wayne; President-Elect, Hubert B. Pirkle, M.D., Rockville; Vice-President, J. V. Pace, M.D., New Albany; Secretary-Treasurer, C. J. McIntyre, Indianapolis; Executive Secretary, Murray A. Auerbach, Indianapolis.

Report of the Massachusetts Trudeau Society

Dr. William R. Martin, *Secretary-Treasurer*

The Boston Trudeau Society was changed to the Massachusetts Trudeau Society at the fall meeting in November, 1945. This change was considered appropriate, as the membership is composed of physicians from the whole State.

The Society holds three meetings a year; in the fall, midwinter and spring. In the spring is the Annual Meeting at which offices for the ensuing year are filled. At the fall meeting we plan to have an outstanding speaker to talk on some special phase of tuberculosis.

Our membership has steadily increased, and at the present time we have 99 members. As the Society is limited to 100 members, it will be necessary in the near future to increase the membership quota. The attendance at meetings has steadily improved, and we now average from 50 to 60 at a meeting. The present officers are: Dr. David Zacks, President; Dr. Richard Sweet, Vice-President; and Dr. William R. Martin, Secretary.

Report of the Michigan Trudeau Society

Dr. W. L. Brosius, *Secretary-Treasurer*

The Michigan Trudeau Society has not planned a spring meeting. Consequently, there is no activity to report since the fall meeting.

A meeting is planned for the early fall of 1946, and it is hoped that it may be made a joint meeting with the Ontario group.

Report of the Minnesota Trudeau Society

Dr. Clarence Siegel, *Secretary-Treasurer*

The following is a report on the activities of the Minnesota Trudeau Society for the year ending June 1, 1946.

A meeting of the Minnesota Trudeau Society was held in Minneapolis, Minnesota, on July 13, 1945. Thirty-five guests and members were present.

An amendment to the constitution was passed, as follows: "The fiscal year shall be the calendar year." This amendment will now be embodied in the constitution and by-laws.

Dr. Davies discussed laws in other states which provided for free care for all tuberculous patients hospitalized, regardless of financial status. A motion was made and seconded that this matter be referred to the legislative committee.

The following scientific program was presented:

Pulmonary Resection in the Tuberculous by Dr. O. T. Claggett of Rochester, Minnesota. Discussion by Dr. T. J. Kinsella of Minneapolis, Minnesota.

Report of the Tri-State Advisory Committee by Dr. E. P. K. Fenger of Oak Terrace, Minnesota.

The annual fall dinner meeting was held in St. Paul, Minnesota, on October 19, 1945. Forty-three guests and members were present. Dr. E. P. K. Fenger gave a report on the Sanatorium Advisory Committee. A motion was made and seconded that two members of that committee be replaced each year by two new members to be appointed by the President of the Society. The two retiring members are to remain as alternates for the coming year. A motion was made and seconded that the Executive Committee be authorized to pay the expenses of outside speakers who come to speak before the Society.

The following officers were elected for the coming year: Dr. T. J. Kinsella, President; Dr. H. C. Hinshaw, Vice-President; Dr. C. Siegel, Secretary-Treasurer.

The following scientific program was presented:

Primary Alveolar Carcinoma of the Lung by Dr. George Roth of St. Paul, Minnesota. Discussion by Dr. E. K. Geer and Dr. K. Ikeda, both of St. Paul.

A case report on *Carcinoma of the Lung* was given by Dr. Earl Craw of Ah Gwah Ching, Minnesota.

Tuberculosis Survey by Dr. E. S. Mariette, Oak Terrace, Minnesota.

The annual winter meeting of the Minnesota Trudeau Society was held in Minneapolis, Minnesota, on January 25, 1946. Thirty-six members and guests were present.

Dr. E. P. K. Fenger gave a report on the Sanatorium Advisory Meeting which was held at Glen Lake Sanatorium. At this meeting ninety-nine selected cases were presented.

A meeting with the Wisconsin and Michigan committees is planned for June at Pembine, Wisconsin. Fifteen men from Minnesota are to go to this meeting.

The following scientific program was presented at the winter meeting.:

Bronchoscopic Aspects of Bronchial Tuberculosis by Dr. S. S. Cohen, of Oak Terrace, Minnesota.

Meig's Syndrone by Dr. John Briggs of St. Paul, Minnesota. Discussion by Dr. E. K. Geer also of St. Paul.

A meeting is to be held by the Minnesota Trudeau Society as guests of the Mayo Foundation at Rochester, Minnesota, on May 3, 1946. The following scientific program is to be presented:

Introductory Remarks by Dr. W. S. Lemon.

Tuberculosis of the Eye by Dr. W. L. Benedict.

Renal Tuberculosis by Dr. E. N. Cook.

Tuberculosis of the Skin by Dr. H. Montgomery.

Anal Tuberculosis by Dr. R. J. Jackman.

Recent Observations in the Experimental Use of Streptomycin by Dr. W. H. Feldman.

Report of the Mississippi Valley Trudeau Society

Dr. John D. Steele, *Secretary-Treasurer*

The 1945 Annual Meeting of the Mississippi Valley Trudeau Society was held at the Edgewater Beach Hotel in Chicago on October 8 and 9, 1945. This meeting was called on short notice after the lifting of bans on conventions following the termination of the war. In spite of the brief time for preparations for the program and short-time notice to the members, the meeting was of excellent quality and well attended. The papers given were of high merit and great variety.

On October 9, 1945, the business session was held with Dr. Loren L. Collins presiding. The minutes of the last meeting were read and approved. Following this Dr. Ezra Bridge, President of the American Trudeau Society, brought greetings to the Mississippi Valley Section from the National organization. After this, Dr. E. S. Mariette, President-Elect, gave a short address on *Rehabilitation.*

The President then called for the recommendations of the Nominating Committee. This Committee, consisting of Dr. J. Arthur Myers, Dr. M. H. Draper and Dr. Raymond H. Runde, presented the following slate of nominations: President-Elect, Dr. John H. Skavlem; Vice-President, Dr. Richard Davison; Secretary-Treasurer, Dr. John D. Steele. These candidates were declared elected by unanimous ballot.

Report of the Missouri Trudeau Society

Dr. D. L. Coffman, *Secretary-Treasurer*

The following is a report on the activities of the Missouri Chapter of the American Trudeau Society for the year ending June 1, 1946.

The regular meeting was held in St. Louis, Missouri, on September 21, 1945.

On February 9, 1946, there was a joint meeting under the sponsorship of this Society with members of the Indiana and Illinois Societies participating. This was a two-day meeting held at the Hotel Coronada, St. Louis, Missouri, and it

consisted of a presentation of consecutive admissions from each of three sanatoria in this district, namely, Robert Koch Hospital, St. Louis, Missouri; Indiana State Sanatorium, Rockville, Indiana; County Sanatorium, Waukeegan, Illinois.

Each of these institutions presented their first 75 admissions admitted during 1944. These were discussed, and it was felt by those in attendance that it was a very worth while meeting.

It was voted to continue these meetings in the future as a yearly event. The date and place have as yet not been decided upon, but it is expected that early in the spring will be the time of choice.

Report of the Southern Trudeau Society

Dr. Jesse B. Naive, *Secretary-Treasurer*

The Southern Trudeau Society is planning to hold a meeting in connection with the Southern Tuberculosis Conference, Jacksonville, Florida, October 3 and 4, 1946.

No doubt that meeting will lead to a schedule of regular meetings, now that travel restrictions are off, a definite program of through-the-year activities and scientific programs at the annual meetings.

Report of the Texas Trudeau Society

Dr. Elliott Mendenhall, *Secretary-Treasurer*

Since the Texas Tuberculosis Association has not had a meeting for the past year, the Texas Chapter of the American Trudeau Society has had no meeting and has not been active.

A meeting is planned for early in the fall of 1946.

Report of the Wisconsin Trudeau Society

Dr. John D. Steele, *Secretary-Treasurer*

The Wisconsin Trudeau Society met at Muirdale Sanatorium, Wauwatosa, Wisconsin, on April 27, 1946. Dr. E. R. Daniels, Vice-President, presided. The Society was entertained at luncheon by the Sanatorium. Fifty physicians were present.

The following officers were elected for a two-year term: President, Dr. A. A. Pleyte, Milwaukee; Vice-President, Dr. H. A. Anderson, Stevens Point; Secretary-Treasurer, Dr. Helen A. Dickie, Madison.

The entire program consisted of a symposium on pneumothorax. The basis for discussion consisted of the presentation of the X-ray and clinical records of 40 consecutive patients who had had pneumothorax recommended at Muirdale Sanatorium subsequent to January 1, 1943. The presentation of the cases was made by Dr. Nathan Grossman. In some cases pneumothorax was not induced;

in others the pneumothoraces were soon abandoned and alternate methods of treatment used; in the remainder pneumothorax was continued satisfactorily.

The discussion of the cases by the audience was free and frank. A great majority of those present agreed on the following points:

1. A waiting period of at least three months, during which the patient should be at bed-rest, is desirable before pneumothorax is induced.
2. If limiting adhesions are present which cannot be successfully severed by an intrapleural pneumonolysis, the pneumothorax should be promptly abandoned and alternate methods of therapy adopted.
3. Pneumonolysis, when necessary, should be performed promptly, preferably within the first month after induction of the pneumothorax.
4. Pneumothorax should not be used for lesions which are predominantly exudative in character.
5. Consideration should be given to primary thoracoplasty (instead of pneumothorax) in predominantly productive lesions of long standing.

NATIONAL TUBERCULOSIS ASSOCIATION
AMERICAN TRUDEAU SOCIETY
Exhibit at Annual Meeting in San Francisco

At the next annual meeting of the National Tuberculosis Association and the American Trudeau Society, June 17 to 20, 1947, in San Francisco, an exhibit will be held. Anybody desiring to participate in this exhibit should communicate immediately with Dr. Sidney J. Shipman, 490 Post Street, San Francisco 2, California, or with Dr. John H. Skavlem, Union Center Life Building, Cincinnati 2, Ohio, and state his requirements as far as space is concerned.

THE AMERICAN ASSOCIATION FOR THORACIC SURGERY

A Report of Its Meeting on May 29, 30 and 31, 1946[1]

RICHARD H. MEADE, JR.[2]

The program of the meeting of the American Association for Thoracic Surgery held on May 29, 30 and 31 in Detroit was in a general way divided into three groups of subjects. In the first was the discussion of war surgery of the chest and a report on chest surgery done in the military hospitals in this country. Among the papers in the second group were those dealing with surgery of the heart and great vessels, thymectomy for myasthenia gravis, pulmonary cysts, the surgical management of carcinoma of the esophagus and vagotomy for peptic ulcer. In the third group were the papers dealing with the surgical treatment of pulmonary tuberculosis.

As Doctor Tuttle is to speak to you this afternoon on War Surgery of the Chest I shall not report on the papers dealing with this subject, except for the one by Dwight Harken on the removal of foreign bodies from the heart. He gave a moving-picture demonstration and reported on his experience with the successful removal of metal fragments from hearts without a death. Thirteen foreign bodies were removed from the chambers of the heart and 55 from the myocardium and pericardium. Lawrence Miscall, in discussion, recorded his experience with 39 operations, also without a fatality. This dramatic surgery was made possible by the perfection of surgical technique and the ability to rapidly replace the blood lost during the procedure.

Among the reports from the military hospitals in this country was one recording a series of 196 lobectomies with one death. Another paper dealt with the surgical management of a wide variety of esophageal lesions including battle injuries and tumors. In the report on the surgical management of traumatic diaphragmatic hernia, it was pointed out that the hernia usually followed some inconspicuous injury. In the Army Chest Center from which this report came no case was seen in which hernia followed the operative repair of a diaphragmatic wound. This is an important observation, as so many men had injuries to their diaphragm which did not necessitate operation and it is likely that many of them will later develop hernias. Another essayist reported on 2 cases of traumatic diaphragmatic hernia in which an erroneous diagnosis of empyema had been made and the herniated stomach drained.

The Direct Approach to Cardiovascular Disease was the subject of the presidential address given by Claude Beck. He summarized his work on chronic cardiac compression and the establishment of a new blood supply for the heart, and spoke of the new era in cardiac surgery which would follow the perfection of a method

[1] Presented before the Medical Section at the 42nd annual meeting of the National Tuberculosis Association, Buffalo, New York, June 11, 1946.

[2] Secretary, American Association for Thoracic Surgery, 55 East Washington Street, Chicago 2, Illinois.

to control the blood-flow through the heart. This method, developed by John Gibbon, Jr., before the war, has been successfully used in cats.

The brilliant results obtained by Blalock in operations on patients with the Tetralogy of Fallot are too well known by now to warrant a discussion of the subject here. He and Helen Taussig reported their experiences with 140 patients. It was possible to compensate for the pulmonary stenosis, by anastomosing one of the large systemic arteries to one of the pulmonary arteries, in all except 3 instances. In these 3 there was an absence of the pulmonary artery on the operated side.

The surgical treatment of the patent ductus arteriosus was presented in two papers by John Jones and Robert Gross. Jones discussed the complications encountered in his series of 61 cases. In addition to a consideration of technical details, he pointed out that the true criteria for determining the presence of reopening of the ductus were the machinery murmur and the characteristic changes in the sound track recording of the heart sounds. Touroff reported that he had demonstrated at operation that the systolic murmur could persist after ligation of the ductus and was due to dilatation of the pulmonary artery. Gross in his paper reported his experience with 133 operations, in the last 90 of which he had successfully divided the ductus in each instance. In the discussion of the subject it was agreed that good results could be expected from simple ligation of the ductus when it was soft and pliable and that ligation was preferable to division when there was associated infection. Altogether 314 operations were reported by the two essayists and three other surgeons, Crafoord of Sweden, Wangensteen and Edgar Davis, with a total mortality of only 6 and with a continuation of the excellent results previously reported. A rare recurrence of the patency of the ductus had been noted.

The surgical management of coarctation of the aorta was presented in moving-pictures by Clarence Crafoord of Sweden. He and Gross had previously reported on the successful treatment of this condition by excision of the narrowed segment and reëstablishment of the continuity of the artery by anastomosis. Thus another vascular anomaly, previously considered a hopeless condition, has been corrected by surgery.

A report by Clagett, of the Mayo Clinic, on 32 patients with myasthenia gravis treated by thymectomy was made. More than half of the patients were cured or helped. Those who had definite tumors did better than the others. In discussion, Blalock emphasized the fact that improvement in these cases was often long delayed after operation.

A series of 44 patients with pulmonary cysts was reported by Moersch; 36 were bronchogenic and, of these, 11 were infected. The other 8 cases were of cystic bronchiectasis. The results of surgical treatment were excellent. The occasional development of carcinoma in a cyst is an added reason for their excision. In 2 of the 36 bronchogenic cysts in this series carcinoma was also found.

Lester Dragstedt reported on his experimental and clinical work on vagotomy in the treatment of peptic ulcer. Remarkable results have been obtained when

there has been no mechanical complication such as pyloric stenosis. This seemingly non-thoracic subject was given a place on our program because of the use of a transthoracic approach in most of the operations and because of the increasing frequency with which surgery of the stomach and lower esophagus has been done through the chest.

The chief discussion of the surgery of pulmonary tuberculosis had to do with the use of pulmonary resection, which is to be presented here by the same men who did so at our meeting and therefore will not be summarized by me.

O'Brien and his associates reported on the use of cavernostomy in certain cases of tuberculosis. In recording their experiences with 74 patients for whom no other surgery seemed possible, they found that 27 per cent became apparently arrested. It was agreed that the procedure still had a definite but very limited field of usefulness.

PULMONARY RESECTION IN THE TREATMENT OF PULMONARY TUBERCULOSIS[1]

Analysis of 88 Patients followed for a Period of Two to Twelve Years after Operation

RICHARD H. OVERHOLT,[2] NORMAN J. WILSON, JOHN T. SZYPULSKI AND LAZARO LANGER

In 1944 two of the authors published their experience in the treatment of tuberculosis with pulmonary resection (1, 2). At that time the preliminary nature of the reports was emphasized as follows: "Any report on pulmonary resection as a form of treatment for tuberculosis must be considered as a preliminary report at this state of our knowledge and experience. Because of the nature of the disease being treated, time and rigid follow-up of these patients will eventually tell the true story."

The purpose of this paper is to analyze a group of 88 patients treated by 92 resections between 1934 and March 31, 1944. The follow-up period ranged from two to twelve years. Seventy-four of these resections have been performed since 1942. Only 18 were performed prior to January 1, 1942. Thus, the duration of time since operation is too short to permit the statistics to be considered as a late follow-up. Only when a large number of patients have been followed for more than five years will the late statistics be truly significant.

March 31, 1944, was chosen as the dividing line for this group of patients for two reasons: By so doing, a minimum follow-up period of two years was made possible. In addition, this date ushered in an era of new techniques. Since then, general anesthesia and the side position of the patient during operation have been abandoned. All except 12 patients have been operated upon in the face-down position and all except 7 under a combination of paravertebral block and local infiltration with novocaine. The last portion of this paper will give a brief summary of the results with these newer techniques.

GENERAL STATISTICS

There were 92 operations upon 88 patients, 4 patients having two resections. In 3 of these, pneumonectomy was performed in two stages. The second resection was indicated by exacerbation of remaining disease following lobectomy. The other patient had both upper lobes resected.

There were 58 pneumonectomies and 34 lobectomies performed upon 74 females and 18 males. The preponderance of left pneumonectomies and of females can possibly be explained by the high incidence (38 per cent) of tuberculous bronchitis in this group of patients. In our experience this complication is more common in women and is seen more frequently on the left side.

[1] Presented before the Medical Section at the 42nd annual meeting of the National Tuberculosis Association, Buffalo, New York, June 11, 1946.

[2] New England Deaconess Hospital, Boston, and Cambridge Tuberculosis Hospital, Cambridge, Massachusetts.

The youngest patient was 15 years of age and the oldest was 57. Five patients were over 50 years of age.

The duration of the disease prior to resection bears special attention. Six patients (6 per cent) had been ill for less than six months and 15 (16 per cent) for less than one year. Twenty-six patients (27 per cent) had their disease for more than five years and 10 (11 per cent) for more than ten years.

Seventy-five of the 92 cases (82 per cent) had a positive sputum at the time of operation. Those with a negative sputum are represented largely by those with tuberculoma and those with residual bronchiectasis following control of their tuberculosis.

At the time of operation 68 patients (74 per cent) were considered to be reasonable risks and 24 (26 per cent) desperate risks. We call special attention to this group of desperate risks because we feel that they have entered surgical statistics for the first time and were previously rejected for collapse therapy measures. The following criteria have determined the classification of a patient as a desperate risk: first, no other form of therapy could be used with expectation of control of the disease; second, every clinician taking care of the patient, in addition to the surgeons, was of the opinion that resection offered the patient his only chance to get well; third, the patient's general condition and the type and distribution of disease were such as to make operation a real hazard. We feel that *any salvage in this group of patients, regardless of how small, can be considered pure gain.*

INDICATIONS

Table 1 gives the indications for resection.

In 7 cases, resection was indicated by the symptoms produced by residual bronchiectasis following the control of the tuberculosis. In 4 cases, bronchiectasis and active tuberculosis coexisted. In the remaining 81, resection was performed as a type of therapy for the tuberculous infection itself.

Thoracoplasty failure was the indication in 16 cases (17 per cent); tuberculous bronchitis was present in 5 of these 16.

Extensive, predominantly unilateral tuberculosis was the most common indication (42 cases, or 46 per cent of the entire series). Of this group, 26 had a complicating tuberculous bronchitis, an incidence of 62 per cent. Most of the patients classified as "desperate risks" are in this group. Many of them had rapidly spreading exudative and caseous-pneumonic lesions. Large tension cavities, multiple cavities throughout the lung, a combination of apical and basal cavities, and predominantly basal distribution of disease were common findings. By and large, they represent a group of patients with extensive, complicated forms of tuberculosis. In a high percentage, thoracoplasty was contraindicated. In those in whom thoracoplasty might have been given a trial, complete collapse would have been required.

We have pointed out in previous papers (1, 2, 3) that it is difficult, if not impossible, to convey an accurate concept by such a categorical list of indications

of the type of case which has been treated by resection. All physicians treating tuberculosis realize that therapeutic measures are used only after the most thorough consideration of each particular case from the beginning of the illness. However, a consideration of the following facts may help to convey a truer picture of the type of patient in this resection series.

(*1*) Thirty-nine patients (42 per cent) had tuberculous lesions in the contralateral lung. (Calcified lesions and primary complexes not included.)

(*2*) Five patients (5 per cent) had had previous collapse therapy of the contralateral lung, 4 with pneumothorax and one with phrenic paralysis. One patient had contralateral pneumothorax at the time of lobectomy. One previously had had a contralateral tuberculous empyema complicating the pneumothorax.

(*3*) One patient had tuberculous empyema on the same side at time of operation.

TABLE 1

Indications

I Associated suppurative disease	11
(a) Tuberculosis controlled	7
(b) Tuberculosis uncontrolled	4
II Post-thoracoplasty uncontrolled disease	16
(a) No endobronchial tuberculosis	11
(b) With endobronchial tuberculosis	5
III Extensive predominantly unilateral tuberculosis	42
(a) No endobronchial tuberculosis	16
(b) With endobronchial tuberculosis	26
IV Upper lobe disease	10
(a) No endobronchial tuberculosis	10
(b) With endobronchial tuberculosis	0
V Basal disease	10
(a) No endobronchial tuberculosis	10
(b) With endobronchial tuberculosis	0
VI Tuberculoma	1
VII Bilateral upper lobe giant cavities	2

(*4*) One patient had a cavernostomy wound draining at the time of operation.

(*5*) Three patients had had a previous lobectomy.

(*6*) Sixteen patients (17 per cent) had been treated by thoracoplasty and 4 of these had also had revisional thoracoplasty.

(*7*) Thirty-five patients (38 per cent) had a complicating tuberculous bronchitis.

(*8*) Only 25 patients (27 per cent) had no collapse therapy on either side prior to resection. The remaining 67 patients (73 per cent) represent a group of collapse therapy failures with the resulting complications and impairment of pulmonary functional reserve.

(*9*) Twenty-six patients (28 per cent) had been ill for more than five years and 10 (11 per cent) for more than ten years. Most of these had been subjected not only to multiple collapse therapy measures but also to years of tuberculous toxemia.

POSTOPERATIVE COMPLICATIONS RELATED TO TUBERCULOSIS FOLLOWING LOBECTOMY

In discussing postoperative complications the entire series has been divided into two groups on the basis of significant variations in technique. Those

patients operated upon between 1934 and January 1, 1942 comprise group 1. During this developmental period pre- and postoperative care, operative technique and the selections of cases were not well standardized. The tourniquet method of handling the hilum was used in 3 cases. The pleural flap method of closing the bronchus was not used routinely. Group 2 consists of those patients operated upon between January 1, 1942 and March 31, 1944. In this series of patients pre- and postoperative care, operative techniques and the selection of cases were fairly well standardized. All patients were operated upon in the conventional side position under general anesthesia—usually cyclopropane.

Table 2 presents the complications that became manifest during the sixty-day postoperative period.

TABLE 2
Lobectomies

Postoperative complications related to tuberculous infection

	GROUP 1 1934 TO JANUARY 1, 1942	GROUP 2 JANUARY 1, 1942 TO MARCH 31, 1944
	7 lobectomies Number	27 lobectomies Number
I Tuberculous wound infection	0	0
II Tuberculous empyema		
(a) With fistula	3	1
(b) Without fistula	0	0
III Nontuberculous empyema		
(a) With fistula	2	0
(b) Without fistula	0	0
IV Fistula		
(a) Temporary	2	1
(b) Permanent	3	1
V Contralateral spread	1	2
VI Contralateral exacerbation	0	0
VII Tuberculosis of chest wall	0	0
VIII Ipsolateral spread	0	1
IX Ipsolateral exacerbation	0	3
X Ulceration of bronchial stump	0	0

Wound infection: There were no wound infections either of a tuberculous or a nontuberculous nature.

Fistula and empyema: Three patients in group 1 had permanent fistulae and, as a result, all 3 developed tuberculous empyemata. One patient in group 2 had a permanent fistula. The only evidence for this was a small cap of air over the lung. The fistula was not recognized and the patient showed no evidence of empyema. He was discharged from the sanatorium one year later. He returned ten months following this with a localized empyema and spread of infection to both lungs secondary to his fistula, and died within a few weeks.

Two patients of group 1 had temporary fistulae and developed nontuberculous empyemata which completely healed following drainage. One patient of group 2 developed a temporary fistula. This was closed with a free muscle graft and

thoracoplasty performed. He did not develop an empyema and is well and working with a consistently negative sputum three years following operation.

It is significant that all empyemata have been associated with fistulae. The lower incidence of both of these complications in the lobectomy series as compared with the pneumonectomy group is due to the rapid and complete reëxpansion of the lung, obliterating the pleural space and giving additional support to the area of bronchial closure.

Contralateral spread and exacerbation: Contralateral spread has occurred in 3 patients, one in group 1, and 2 in group 2. Two of these patients died in the postoperative period as a result of this complication. The other has stabilized the lesion and is completely well with negative sputum by guinea pig inoculation.

Contralateral exacerbation has occurred in none of the patients in spite of the fact that contralateral lesions were present in 14 prior to operation.

Ipsolateral spread and exacerbation: Ipsolateral spread has occurred in only one patient.

Ipsolateral exacerbation has occurred in 3 patients (11 per cent), all in group 2. The high incidence of this complication as a late manifestation will be pointed out later.

In general, table 2 demonstrates that the incidence of all postoperative complications in group 2 was reduced by improved operative technique and greater experience. Empyema and fistula were almost eliminated. Contralateral spread, which occurred in 7 per cent of the patients, and ipsolateral exacerbation, which occurred in 11 per cent, remained the greatest threats to the patient following lobectomy. Later in this paper, results of the last two years with local anesthesia and the face-down position of the patient during operation will be presented. Contralateral spread has occurred in only one patient and ipsolateral exacerbation in none of the 35 consecutive lobectomies with these newer techniques.

POSTOPERATIVE COMPLICATIONS RELATED TO THE TUBERCULOUS INFECTION FOLLOWING PNEUMONECTOMY

Table 3 presents the postoperative infectious complications following pneumonectomy.

Tuberculous wound infection: There were no tuberculous wound infections and no major wound sepsis of a nontuberculous nature.

Fistula and empyema: In group 1, 2 patients developed bronchial fistula. One of these had a tuberculous empyema prior to resection. The other developed tuberculous empyema as a result of the fistula. There was only one nontuberculous empyema. This was not associated with fistula.

In group 2, 2 patients (4 per cent) developed fistula and both had tuberculous empyema as a result. One patient had tuberculous empyema not associated with fistula. This was discovered at the time of autopsy on the fifty-third postoperative day. There had been no clinical evidence of this complication. Four patients had nontuberculous empyema none of which was associated with fistula.

It is worthy of note that in these groups of patients tuberculous empyema was

associated with fistula in all except one case. In contradistinction to this, fistula was not present in any case with a nontuberculous empyema. In fact, following pneumonectomy in the tuberculous patient we have never seen a fistula that did not result in a tuberculous empyema, nor have we ever seen a nontuberculous empyema, associated with a fistula.

Contralateral spread and exacerbation: As table 3 shows, all serious complications have been minimized in group 2 except contralateral spread. This occurred in 19 per cent of the cases and remained the greatest threat to the tuberculous patient coming to resection. As will be pointed out later, the face-down position of the patient during operation and local anesthesia have been used during the

TABLE 3
Pneumonectomies

Postoperative complications related to tuberculous infection

	GROUP 1 1934 TO JANUARY 1, 1942	GROUP 2 JANUARY 1, 1942 TO MARCH 31, 1944
	11 pneumonectomies Number	47 pneumonectomies Number
I Tuberculous wound infection	0	0
II Tuberculous empyema		
(a) With fistula	1	2
(b) Without fistula	0	1
III Nontuberculous empyema		
(a) With fistula	0	0
(b) Without fistula	1	4
IV Fistula		
(a) Temporary	0	0
(b) Permanent	2	2
V Contralateral spread	1	9
VI Contralateral exacerbation	0	2
VII Ulceration of bronchial stump	0	1
VIII Tuberculosis of chest wall	0	3
IX Contralateral spread secondary to fistula	1	1

last two years in an attempt to reduce the incidence of this complication. Contralateral spread is the result of spilling infected secretions and debris from the bad to the good lung during operation. Those with large amounts of sputum are most likely to suffer this complication.

Contralateral exacerbation during the postoperative period occurred in only patients, even though contralateral lesions were present in 25.

Ulceration of bronchial stump: This was discovered in only one patient during the postoperative period. This complication usually becomes evident later.

Tuberculosis of chest wall: This does not refer to tuberculous wound infections but to the presence of tuberculous changes in the chest wall tissues discovered only after making the incision for the post-pneumonectomy thoracoplasty. In spite of this, thoracoplasty was completed. All 3 wounds healed by primary intention and have never manifested any signs of infection.

LATE COMPLICATIONS RELATED TO TUBERCULOUS INFECTION FOLLOWING LOBECTOMY

Table 4 gives the late complications related to the tuberculous infection following lobectomy.

There were 2 late tuberculous wound infections, both occurring in the same patient. This patient had had bilateral upper lobectomy for bilateral, giant cavities.

There was only one late nontuberculous empyema. This occurred in a patient who had had a localized Schede thoracoplasty for nontuberculous empyema prior to lobectomy. An *empyema necessitatis* developed four years after operation. This has been drained and is now closing in rapidly.

No fistula has developed late.

TABLE 4

Lobectomies (34)

Late complications related to tuberculous infection

		Number
I	Tuberculous wound infection	2
II	Tuberculous empyema	0
	(a) With fistula	0
	(b) Without fistula	0
III	Nontuberculous empyema	1
	(a) With fistula	0
	(b) Without fistula	1
IV	Bronchial fistula	0
V	Contralateral spread secondary to fistula	1
VI	Contralateral exacerbation	0
VII	Contralateral spread	1
VIII	Contralateral lesion developed	2
IX	Ipsolateral spread secondary to fistula	1
X	Ipsolateral exacerbation	11
XI	Ulceration of bronchial stump	2

Contralateral spread and ipsolateral spread have occurred in the same patient secondary to a bronchial fistula and localized empyema. This was the case described under postoperative complications in which the small fistula was not recognized postoperatively.

Contralateral lesions have developed in 2 patients whose contralateral lung was clear prior to resection. This complication occurred a few months following operation in one case and was controlled by pneumothorax. The patient is living and well with a negative sputum five years after operation. The other patient developed her lesion five years after lobectomy. This progressed over a period of one and two-thirds years during which time no treatment was given. Death resulted six and two-thirds years following resection. In neither case was there any evidence of reactivation of disease on the side of operation.

Ipsolateral exacerbation has occurred in 11 cases (32 per cent). This is the most common postoperative and late complication following lobectomy. We feel that it is caused by the following factors:

(*1*) Error in judgment as to the extent and type of disease left in the remaining lobes.
(*2*) Trauma to residual tuberculous foci during operation and during reëxpansion of the lung.
(*3*) Continued overdistension of remaining pulmonary tissue which not only places strain on the remaining tuberculous foci but prevents the contractibility of scar tissue so necessary in the healing process.

Thus, in later years, we have been more careful about the amount and type of disease we have been willing to leave behind in the other lobes. We also advocate routine thoracoplasty following upper lobectomy to return the remaining lung tissue to approximately its normal volume. In our experience, most exacerbations have occurred in those patients who have had either no collapse therapy following resection or who have had phrenic paralysis. This latter procedure seems to give little or no protection following lobectomy. It may be that thoracoplasty should be used also, following lower lobectomy.

Ulceration of the bronchial stump occurred in 2 cases. A pathological study of both surgical specimens revealed extensive tuberculous bronchitis in the resected lobes.

LATE COMPLICATIONS RELATED TO TUBERCULOUS INFECTION FOLLOWING PNEUMONECTOMY

Table 5 gives the late infectious complications in patients treated by pneumonectomy.

TABLE 5

Pneumonectomies (58)

Late complications related to tuberculous infection

	Number
I Tuberculous wound infection	1
II Tuberculous empyema	1
(a) With fistula	1
(b) Without fistula	0
III Nontuberculous empyema	0
IV Bronchial fistula	1
V Contralateral exacerbation	4
VI Contralateral spread secondary to fistula	1
VII Contralateral disease developed	6
VIII Contralateral pleurisy with effusion	2
IX Ulceration of bronchial stump	5

One tuberculous wound infection occurred in a patient who had a pleural fluid positive for tubercle bacilli prior to pneumonectomy.

One late empyema associated with fistula has been encountered; this occurred nine months following resection. This patient also had a positive pleural fluid prior to resection. A contralateral spread secondary to the fistula has taken place in the same patient.

Contralateral exacerbation has occurred in 4 patients. Prior to operation, 3 of these patients had productive lesions and one had a mixed lesion in the contra-

ateral lung. Two of the 4 are dead and 2 have unstable lesions according to X-ray appearance but are asymptomatic and have negative sputum.

Contralateral new disease has developed in 6 patients. Two of these had contralateral lesions prior to resection but the new disease occurred in new areas of the lung and was not associated with exacerbation of the old foci. New disease developed in 4 patients who had had no contralateral lesion. In one of these, the parenchymal lesions represented a spread from a stump ulceration. The source of the infection in the other 3 is obscure. Of these 6 patients, one is living and well, one has an unstable lesion according to X-ray appearance, 3 are dead, and one is dying.

Contralateral pleurisy with effusion has developed in 2 patients. Neither patient has developed a parenchymal lesion and both are well; they have consistently negative sputum examinations. The fluid was positive on guinea pig inoculation in one case and negative in the other.

Ulceration of the bronchial stump has occurred in 5 patients (9 per cent). This complication may occur early or late. For this reason, routine bronchoscopic examination is advocated six weeks and again six months following resection. A recurrence of positive sputum should always make one suspicious of stump ulceration. Three of these 5 patients were treated promptly and intensively with 30 per cent silver nitrate every two weeks. One patient refused bronchoscopic treatments and still has ulceration of the bronchial stump. The other is now having local therapy with silver nitrate and appears to be responding.

FATALITY STATISTICS—LOBECTOMY

Of the 34 cases, 3 died during the postoperative period, a fatality rate for both groups of 9 per cent (table 6). In group 1 the fatality rate was 29 per cent and in group 2, 4 per cent. This reduction in operative mortality was the result of increased experience, better operative technique and more careful selection of cases.

Two of the 3 patients were considered to be desperate risks at the time of resection. One had been ill for ten years and had been under bilateral collapse therapy. Tuberculous empyema also complicated the contralateral pneumothorax. He died of contralateral spread and pulmonary insufficiency. The other desperate risk patient was 57 years old. A complicating stenosis of the right intermediate bronchus was present and a right middle and lower lobectomy was performed. A fistula and empyema resulted and the patient developed bizarre central nervous system symptoms prior to his death. The cause of death was never satisfactorily explained. To-day, we would perform a pneumonectomy on this type of case. The other patient died as a result of a massive, contralateral spread. She was an excellent risk. The indication was thoracoplasty failure.

There have been 4 late deaths, making the total case fatality 21.2 per cent (see table 7). One other patient died fifteen months following the completion of pneumonectomy (two-stage). She is classified as a late death after pneumonectomy but her death was indirectly the result of her original lobectomy. Thus, 8 of the original 33 patients are dead.

Table 7 analyzes the late deaths following lobectomy. This table is self-explanatory but the following descriptions will be helpful: The patient (R. B.) with the bronchopleural fistula was the one previously described in this paper in whom the fistula was not

TABLE 6

Lobectomy—Three postoperative deaths

NAME	AGE	DURATION OF ILLNESS	PREVIOUS THERAPY	TUBERCULOUS BRONCHITIS	INDICATION	RISK*		OPERATION	POST-OPERATIVE DAY OF DEATH	CAUSE
						R. R.	D. R.			
C. B.	37	10 years	Pnthx, plombage, thplsty, 2 revisions, cavernostomy contralat. pnthx.	?	IA		+	R. U. and M.	31st	Contralateral spread, pulmonary insufficiency
L. M.	57	2 years	0	+	IIIB		+	R. L. and M.	32nd	Fistula, empyema, c. n. s. symptoms
T. B.	24	22 months	Pnthx, thplsty	0	IIA	+		L. U. L.	5th	Contralateral spread

*R. R. = Reasonable risk.
D. R. = Desperate risk.

TABLE 7

Lobectomy—Four late deaths

NAME	AGE	DURATION OF ILLNESS	PREVIOUS THERAPY	TUBERCULOUS BRONCHITIS	INDICATION	RISK		OPERATION	SURVIVAL PERIOD	CAUSE OF DEATH
						R.R.	D.R.			
L. C.	22	5 years	Pnthx, phrenic thplsty	?	IA	+		L. L. L.	6⅔ years	Contralateral tuberculosis
R. B.	37	16 months	Pnthx	0	IV	+		R. U. L.	23 months	Broncho-pleural fistula with bilateral spread
M. L.	24	22 months	Bilateral pnthx, rt. phrenic, r. u. lobectomy	0	VIII		+	L. U. L.	23 months	Bilateral tuberculosis
E. J.	22	11 months	Phrenic	0	IV	+		R. U. L.	6½ months	Ipsolateral exacerbation indicated completion of pneumonectomy. Patient died night of operation of pulmonary edema.

recognized postoperatively. The patient classified as a desperate risk was the one with bilateral, giant cavities treated by bilateral upper lobectomy. The last patient died the night of her second operation of pulmonary edema. This was proved by autopsy. Her death was definitely attributable to poor judgment as to the amount of saline solution given and the speed at which it was given.

Thus, all the postoperative deaths and all but one of the late deaths following lobectomy were caused by tuberculous complications.

FATALITY STATISTICS—PNEUMONECTOMY

Of the 58 patients treated with pneumonectomy, 13, or 22 per cent, died during the sixty-day postoperative period. The operative fatality in group 1 was 27 per cent and in group 2 it was 21 per cent.

There have been 11 late deaths making the total case fatality 41 per cent.

Analysis of postoperative deaths: Table 8 analyzes the causes of the postoperative deaths. This analysis proves to be quite interesting in that only 5 of the 13 deaths were caused by complications related to their tuberculous infection. Three of these patients died of contralateral spread, one of contralateral exacerbation, and one of a massive spread secondary to a bronchial fistula. The remaining 8 patients died of complications related to associated diseases and the surgical problem of pulmonary resection as follows:

(*1*) One patient died on the fourth day of diabetic coma. The carbon dioxide combining power of the blood prior to death was 19 vol. per cent. Autopsy revealed no other complication.
(*2*) Two patients died of pulmonary insufficiency.
(*3*) One patient died of paroxysmal heart action on the first postoperative day. The irregular pulse developed while the nurse was taking the morning pulse and the patient died a few minutes later. Autopsy revealed no other cause of death.
(*4*) One patient died on the second postoperative day of circulatory collapse. Up until this time her condition had been good. There were no signs of respiratory distress.
(*5*) One patient died on the fifteenth postoperative day of pulmonary embolus.
(*6*) One patient died a few hours after operation of shock.
(*7*) One patient developed cardiac standstill following the postoperative bronchoscopy. He had shown no signs of shock during the operation. He never regained consciousness and died on the fourth postoperative day.

A further analysis reveals the following facts concerning this group of 13 patients who died postoperatively (see table 8):

(*1*) Only 5 of these patients were considered to be reasonable risks for operation. In our opinion, the other 8 were truly desperate risks.
(*2*) Two patients were in the older age group, being 49 and 54 years of age, respectively.
(*3*) The duration of illness in 4 patients was over five years and in 3 patients was over ten years. One of these patients had been ill for nineteen years.
(*4*) Nine of the 13 patients had a complicating tuberculous bronchitis. These were all fibro-stenotic and ulcero-stenotic in type.

TABLE 8

Pneumonectomy—Analysis of 13 postoperative deaths

NAME	AGE	DURATION OF ILLNESS	PREVIOUS THERAPY	TUBERCULOUS BRONCHITIS	INDICATION	RISK		SIDE OF OPERATION	POSTOPERATIVE DAY OF DEATH	CAUSE OF DEATH
						R. R.	D. R.			
R. Y.	28	6⅔ years	Phrenic, thplsty, revision	?	IIA	+		R.	4th	Diabetic coma
B. L.	33	10 years	0	+	IIIB		+	L.	4th	Contralateral spread
V. N.	30	3 years	Pnthx, phrenic, thplsty	+	IIB		+	R.	4th	Pulmonary insufficiency
J. C.	54	4 years	0	+	IIIB		+	L.	53rd	Contralateral exacerbation
S. A.	25	5 months	0	0	IIIA		+	L.	1st	Paroxysmal heart action
M. McP.	32	2¼ years	Pnthx, contralateral phrenic	+	IIIB		+	R.	2nd	Circulatory collapse
A. B.	39	11 years	Pnthx	+	IIIB	+		R.	15th	Pulmonary embolus
M. F.	30	4 years	Pnthx, thplsty	+	IIB		+	R.	Day of operation	Postoperative shock
J. G.	49	19 years	Thplsty	+	IIB		+	R.	19th	Pulmonary insufficiency
R. P.	33	4½ years	Pnthx, thplsty	0	IIA	+		R.	4th	Cardiac standstill following postoperative bronchoscopy. Never regained consciousness
J. M.	37	3 years	Thplsty	0	IIA	+		L.	64th	Contralateral spread
A. K.	22	3 years	Bilateral pnthx	+	IIIB		+	L.	6th	Contralateral spread
G. P.	41	2¼ years	0	+	IIIB	+		L.	18th	Fistula, empyema, contralateral spread

(*5*) The indication for pneumonectomy in 6 cases was thoracoplasty failure. In the remaining 7, it was extensive, predominantly unilateral disease. Of these last 7 patients, 2 could have been treated by extensive thoracoplasty but pneumonectomy was elected because of the presence of marked fibrotic stenosis of the bronchus. The remaining 5 could never have been treated by any form of therapy other than pneumonectomy for the following reasons: Four of them had totally destroyed lung by extensive, caseous disease of pneumonic type distal to bronchial lesions. The other patient who had been ill for only five months had a caseous pneumonic lesion involving the entire left lung.

Analysis of late deaths: Table 9 analyzes the 11 late deaths following pneumonectomy. Seven of the 11 died as a result of contralateral tuberculosis. The contralateral disease was the result of postoperative spreads in 2 of these, of exacerbation of previously existing foci in 2 cases, and of the development of new disease in 3. One patient died of a combination of contralateral spread, fistula, empyema, amyloidosis and tuberculous enteritis. Another patient died suddenly on the third day following plastic closure of a bronchial fistula. These 9 deaths were directly related to the tuberculous infection. The remaining 2 deaths were not related to the tuberculous infection. One patient died suddenly while shopping nineteen months following operation. Prior to this time she had been completely well with a persistently negative sputum. The other patient died six months following operation of empyema, contralateral nontuberculous pneumonia, and uremia.

Further analysis of this group of patients brings out the following facts:

(*1*) Six of the 11 had been considered desperate risks at the time of operation. Only 5 were reasonable risks.

(*2*) Six of the 11 had a complicating tuberculous bronchitis.

(*3*) The indications for operation in the first case (C. C.) were pulmonary abscess, bronchiectasis and tuberculosis complicated by a tight, fibrous stenosis of the main bronchus. In the remaining 10, the indication for pneumonectomy was extensive, predominantly unilateral disease, 5 of which were complicated by tuberculous bronchitis. All 10 patients had active lesions at the time of resection. Only 4 had a mixed type of infiltration and these were predominantly exudative. Thoracoplasty might have been tried in 2 of these with small hope of success but the other 2 had predominantly lower lobe disease. The remaining 6 patients had extensive, exudative and caseous lesions which in themselves contraindicated thoracoplasty.

PRESENT CLINICAL STATUS OF THE THIRTY-THREE PATIENTS TREATED WITH LOBECTOMY

Table 10 presents the present clinical status of the 33 patients treated with lobectomy between 1934 and March 31, 1944. This represents a follow-up of from two to twelve years. The table separates the patients into two groups. The follow-up period for group 1 is from four to twelve years and for group 2 from two to four years. This classification has been based upon reports during the past four months from the physicians now taking care of these patients.

Of the entire 33 patients, 14, or 42 per cent, are clinically well and have con-

TABLE 9

Pneumonectomy—Analysis of late deaths

NAME	AGE	DURATION OF ILLNESS	PREVIOUS THERAPY	TUBERCULOUS BRONCHITIS	INDICATION	RISK		SIDE OF OPERATION	SURVIVAL PERIOD	CAUSE OF DEATH
						R. R.	D. R.			
C. C.	28	14 months	0	+	IB		+	L.	6 months	Empyema, pneumonia, uremia
V. D.	28	5 years	Phrenic	+	IIIB		+	R.	19 months	Died suddenly on street
N. S.	34	10 years	Pnthx, phrenic	+	IIIB	+		R.	2½ years	Died suddenly three days following plastic closure of broncho-pleural fistula
S. B.	15	10 months	Pnthx	0	IIIA	+		R.	16 months	Contralateral tuberculosis
E. C.	53	1 year	0	0	IIIA	+		L.	31 months	Contralateral tuberculosis
J. G.	29	3½ years	R. L. lobectomy, phrenic	0	IIIA		+	R.	15 months	Contralateral tuberculosis
E. C.	23	13 months	Pnthx	+	IIIB	+		L.	31 months	Contralateral tuberculosis
D. Q.	29	1 year	Pnthx, phrenic	0	IIIB	+		R.	2 years	Contralateral tuberculosis
E. G.	33	8 years	Pnthx, phrenic	+	IIIB		+	L.	15 months	Contralateral tuberculosis
D. H.	25	6 years	Pnthx	+	IIIA		+	L.	4 months	Contralateral spread, empyema, broncho-pleural fistula
C. B.	22	1½ years	Phrenic	0	IIIA		+	R.	3 years	Contralateral tuberculosis

sistently negative sputum. Only one of these has a questionably unstable lesion according to roentgenograms. This is in the region of an old infiltration in the contralateral lung which was previously treated with pneumothorax.

There is considerable disagreement about whether or not this lesion has changed in appearance in recent months. Twelve of these patients are completely well on full activity. Two are still on modified activity under observation at home.

One patient is clinically well but has a positive sputum. We feel that the source of the positive sputum is a bronchial ulceration although none is visible on bronchoscopic examination at present. She is at home on modified activity.

Four patients are classified as living with progressive disease as a result of ipsolateral exacerbation. Two of these are now having thoracoplasty. We hope to perform a second resection on the other 2. It is possible that we may be able to salvage all 4 of these patients, as they still have clear contralateral lungs.

A program of right upper lobectomy and left thoracoplasty had been proposed for one patient. The right upper lobectomy was performed without complica-

TABLE 10

Present clinical status of 33 patients following lobectomy

	GROUP 1 1934 TO JANUARY 1, 1942	GROUP 2 JANUARY 1, 1942 TO MARCH 31, 1944	TOTAL	
	7 patients Number	26 patients Number	33 patients	
			Number	Per cent
I Clinically well with negative sputum	2	12	14	43
II Clinically well with positive sputum	0	1	1	3
III Living with progressive disease	1	3	4	12
IV Came to second resection	1	6	7	21
V Refused contralateral thoracoplasty		1	1	3
VI Dead	3	3	6	18

tion. She then refused the left thoracoplasty and left the sanatorium against advice. She is still living but has a positive sputum as a result of the open cavity in the left upper lobe.

There were 3 postoperative deaths and 3 late deaths in those treated by lobectomy, a total of 6 of 33, or 18 per cent. In addition, 2 patients who had a second resection (two-stage pneumonectomy) have died. Thus, a total of 8 of the original 33 patients (24 per cent) are dead.

Seven patients (21 per cent) have had a second resection as a result of ipsolateral exacerbation of disease. The following has been the fate of these cases:

(*1*) One patient has a consistently negative sputum but is a respiratory cripple as a result of asthma, pulmonary emphysema, and residual bronchiectasis in the remaining lung.

(*2*) One patient is living with progressive disease.

(*3*) One patient is clinically well but has an occasional positive sputum (question of stump ulceration).

(*4*) Two patients have died. One died the night of operation of pulmonary edema. The other died fifteen months following resection of contralateral tuberculosis.

(*5*) Two patients are clinically well with negative sputum. When these 2 are added to the 14 in table 10, a total of 16 (49 per cent) of the original 33 patients are clinically well with negative sputum.

PRESENT CLINICAL STATUS OF THE FIFTY-EIGHT PATIENTS TREATED WITH PNEUMONECTOMY

Table 11 presents the present clinical status of the 58 patients treated by pneumonectomy between 1934 and March 31, 1944. The follow-up periods are the same for the two groups as described for the lobectomy series.

Twenty-eight (48 per cent) of the 58 patients are clinically well with negative sputum. Of these, only 3 have unstable lesions according to roentgenograms.

TABLE 11

Present clinical status of 58 patients following pneumonectomy

	GROUP 1 1934 TO JANUARY 1, 1942	GROUP 2 JANUARY 1, 1942 TO MARCH 31, 1944	TOTAL	
	11 patients Number	47 patients Number	58 patients	
			Number	Per cent
I Clinically well with negative sputum	4	24	28	48
II Clinically well with positive sputum	0	1	1	2
III Living with progressive disease	0	4	4	7
IV Respiratory cripple	1		1	2
V Dead	6	18	24	41

Twenty-four of the 28 are completely well on full activity. Four are still under observation at home on modified bed-rest.

One patient is clinically well but has a positive sputum as a result of bronchial stump ulceration.

Four patients are living with progressive contralateral disease. Three of these will eventually die of their tuberculosis. The other has an extremely small lesion that is now resolving on bed-rest at home.

Twenty-four patients (41 per cent) are dead. There were 13 postoperative and 11 late deaths.

The patient classified as a respiratory cripple is the same one previously described in the lobectomy series. Her pneumonectomy was performed in two stages.

RESULTS DURING PAST TWO YEARS

Table 12 presents the results of the past two years during which time paravertebral block and local infiltration with novocaine have supplanted general

anesthesia, and the face-down position of the patient during operation has replaced the old conventional side position. Both of these measures were originally conceived in an attempt to reduce the number of contralateral spreads. We consider the face-down position of the patient during operation as one of the most significant advances in the technique of pulmonary resection in recent years. This is especially true if resections are being performed for tuberculosis.

Lobectomy: Lobectomy was performed in 35 patients with 2 (6 per cent) postoperative deaths. One patient died of operative shock and the other died

TABLE 12

Results during past two years using face-down position and local anesthesia

	LOBECTOMY	PNEUMONECTOMY
	35 cases Number	69 cases Number
A. Postoperative complications*		
(1) Tuberculous wound infection	0	4
(2) Tuberculous empyema without fistula	0	5
(3) Nontuberculous empyema	0	1
(4) Fistula	0	2
(5) Contralateral spread	1	7
(6) Contralateral exacerbation	0	5
(7) Ipsolateral spread	1	
(8) Ipsolateral exacerbation	0	
(9) Tuberculosis of chest wall	0	2
B. Fatality		
(1) Operative fatality*	2	9
(2) Total case fatality	4	12
C. Present clinical status		
(1) Clinically well with negative sputum	20	33
(2) Clinically well with positive sputum	3	9
(3) Living with progressive disease	0	4
(4) Dead	4	12
(5) Too recent to classify	7	11
(6) Came to second resection	1	

* All complications and deaths occurring within sixty days are listed as postoperative. Those occurring after sixty days are listed as late.

suddenly a few hours after operation. The cause of death was not determined as autopsy was refused.

Postoperative complications have occurred in only 2 patients, a contralateral spread in one, and an ipsolateral spread in the other. We should like to call special attention to the fact that ipsolateral exacerbation has been eliminated as a postoperative complication. It has occurred in only 2 cases as a late complication. Attention has been called to the high incidence of ipsolateral exacerbation in the earlier groups. We feel that the lowered incidence of this complication is the result of more careful appraisal of the extent and type of disease left behind in the other lobes and increased use of post-lobectomy thoracoplasty to relax the remaining lung tissue. Fistula and empyema were eliminated.

Fifty-seven per cent of the lobectomy series are clinically well with negative sputum. Twenty per cent have been operated upon since January 1, 1946, and are listed as "Too recent for classification." Four patients (11 per cent) are dead.

Pneumonectomy: Pneumonectomy was performed on 69 patients with 9 (13 per cent) postoperative deaths. There have been 3 late deaths making the total case fatality 17 per cent.

Attention is called to the increase in the incidence of wound infection and tuberculous empyema. The increase in these complications has resulted from operative contamination following pneumonotomy and a practice of dividing the bronchus early in the operative procedure during a retrograde dissection of the hilum in an attempt to prevent contralateral spread. We have now abandoned these procedures because of the increase in infectious complications unless we are dealing with an extremely adherent lung and giant cavities. Under these circumstances, it may be better to risk contamination of the pleura rather than to risk flooding of the contralateral lung with secretions and debris.

The incidence of contralateral spread has been reduced to 10 per cent. We feel that the face-down position has been responsible for this.

Forty-eight per cent of the patients are clinically well with negative sputum. Eleven patients (16 per cent) have been operated upon since January 1, 1946, and are listed as "Too recent to classify." Thirteen per cent are clinically well with positive sputum and 6 per cent are living with progressive disease.

The reduction in operative mortality to 13 per cent is significant, since the type of case accepted for operation during the past two years has been just as serious, if not more so, than that accepted during the previous years. More and more collapse therapy failures and last resort cases are finding their way into resection series. The influence of this on statistics can be readily seen when the cases are analyzed. Of the 9 patients who died postoperatively, only 2 were considered as reasonable risks and 7 were rated as desperate risks. Sixteen of the 69 patients in the pneumonectomy series were classified as desperate risks, 53 as reasonable risks. Thus, the operative mortality in reasonable risk cases was 4 per cent and in the desperate risk group 44 per cent. These facts must be considered in analyzing statistics. The type of case being treated is of utmost importance. In considering patients for operation, the surgeon must constantly weigh the risk of the operation against the risk of the disease untreated.

THE PROBLEM OF THE CONTRALATERAL LUNG

The evaluation of the condition of the contralateral lung is of utmost importance when pulmonary resection is contemplated in the tuberculous patient. The criteria in respect to a contralateral lesion must be more rigid when pneumonectomy is anticipated than when lobectomy is to be performed. Following pneumonectomy, bed-rest alone must be relied upon to control the remaining lesion. Contralateral pneumothorax or phrenic paralysis may be employed either before or after lobectomy. A progressive contralateral lesion contraindicates resection. However, we do not believe that the contralateral lung must

be absolutely free of involvement. In patients with bilateral disease, the risk of the contralateral lesion must be weighed against the threat of the ipsolateral disease. For instance, in a patient with a fatal type of disease in one lung, it may be justifiable to take a chance even with an unstable contralateral lesion.

Twenty-five of the 58 patients treated with pneumonectomy had contralateral lesions. Most of these were minimal in extent. A few were moderately ad-advanced. According to the appearance on serial roentgenograms, 8 of the lesions were classified as mixed, 13 as productive and 4 as fibrotic in type. In this group, exacerbation of the contralateral lesion occurred in 6 cases, 2 during the postoperative period and 4 late. Four of these lesions were classified preoperatively as productive and 2 as mixed type of infiltration. Two patients have developed disease in new areas without any evidence of exacerbation of preëxisting lesions. Thus, 17 of the 25 contralateral lesions have shown no exacerbation and have withstood the test of both pneumonectomy and the increased postoperative stress.

Thirty-three of the 58 patients treated with pneumonectomy had no contralateral disease. Four of these have developed new disease in the contralateral lung. In one case this represents a spread from a bronchial stump ulcer. In the other 3 the source of infection remains obscure.

In the lobectomy series of 34 cases, 14 had contralateral lesions, 5 mixed, 5 productive and 4 fibrotic in type. Thirteen of these have shown no tendency to break down. Exacerbation has occurred in only one patient and this was during the postoperative period. Twenty of this group of patients had no contralateral disease prior to resection. Two new lesions have developed in these patients. A spread from the opposite lung has occurred in another.

Thus, of the entire 92 cases which came to either lobectomy or pneumonectomy, 39 had contralateral lesions. Exacerbation has occurred in 7 and new disease has developed in 2. Thirty of the 39 contralateral lesions (76 per cent) have either remained stable or have become stable.

THE PROBLEM OF TUBERCULOUS BRONCHITIS

The evaluation of the condition of the bronchial tree is as important as that of the parenchyma of the lung prior to resection. Tuberculous bronchitis, either active or inactive, has not been considered a contraindication to resection. On the contrary, it has often strengthened the indication for resection. It must be considered in determining the extent of resection as ideally both the parenchymal and the bronchial foci should be removed.

Thirty-five, or 38 per cent, of the patients in this series had bronchial lesions visible through the bronchoscope. They were classified as follows: submucosal 5; ulcerative 4; ulcero-stenosis 10; fibro-stenosis 16.

The high incidence of tuberculous involvement of the major bronchi as revealed by pathological study of surgical specimens has previously been reported (4, 5). This work was done by Dr. William Meissner. This study showed that 50 per cent of the main bronchi and 86 per cent of the segmental bronchi in pneumonectomy specimens showed pathological evidence of tuberculosis. In the lobectomy specimens 71.6 per cent showed involvement of the segmental bronchi. This

evidence has demonstrated that regardless of bronchoscopic findings, bronchial sutures placed during pulmonary resection are almost always in tissues involved, at least microscopically, with tuberculosis.

In spite of the high incidence of tuberculous bronchitis in this series and the above pathological evidence, ulceration of the bronchial stump has occurred in only 8 patients, in 6 following pneumonectomy and in 2 following lobectomy. This has been the cause of lobectomy failure in 2 cases. None of the patients with stump ulceration have developed fistula.

Five of the ulcers following pneumonectomy have been treated with silver nitrate. Four are clinically well with negative sputum and have no evidence of residual ulceration. The other patient has just completed a series of treatments. Her sputum is negative and only questionable mucosal changes remain. The other patient has refused regular treatment. The ulceration following lobectomy in 2 patients has also been treated in similar fashion. One failed to respond. The evidence of ulceration has disappeared in the other but her sputum remains positive.

As a group, patients with endobronchial disease present a serious problem. Not only do they have the bronchial factor to contend with but they also have, as a rule, very extensive and active parenchymal disease. Sixteen of the 35 patients with bronchial tuberculosis were truly desperate risks. Sixteen patients have died; 11 in the postoperative period and 5 later. Three are living with progressive disease. One is clinically well but has a positive sputum. Fifteen patients are clinically well with negative sputum.

SPUTUM CONVERSION

Because the patients have originated from so many different sources, we have had to rely upon reports from physicians in private practice and numerous sanatoria for data concerning sputum conversion. Forty-two of the 58 living patients have been classified by them as negative. The following is a summary of the data we have concerning the type of sputum examination used in these 42 patients:

(*1*) In 12 patients the sputum is negative by seventy-two hour concentrate.
(*2*) In 3 patients the sputum is negative by culture of a seventy-two-hour specimen.
(*3*) In 5 patients the sputum is negative by guinea pig inoculation.
(*4*) In 3 patients the sputum is negative by twenty-four hour concentrate.
(*5*) In 3 patients the sputum is negative by direct smear.
(*6*) In one patient the bronchoscopic specimen is negative.
(*7*) Three patients have negative gastric specimens.

Thus, 24 patients are negative by seventy-two hour concentrate or more rigid sputum examinations. Six patients are negative by methods less rigid than seventy-two hour concentrate. The remaining 12 patients are classified as having no expectoration and gastric specimens have not been examined.

DISCUSSION

Although pulmonary resection has been used with increasing frequency during the past decade in the treatment of tuberculosis, most of our knowledge has been

developed in the past three or four years. For instance, only 18 patients in this series were operated upon more than four years ago. It seems quite evident, therefore, that any report on this subject, at present, must be considered as preliminary in character.

It is important to realize that the rapid growth of pulmonary resection as a form of treatment for tuberculosis has been due largely to the fact that it was needed. The old law of supply and demand was at work. In recent years the limitations as well as the usefulness of the various collapse therapy procedures have been more keenly appreciated. Their relative ineffectiveness in the control of many tuberculous lesions is now generally recognized. This is especially true of patients with endobronchial tuberculosis, extensive basal disease, tension cavities, and in exudative and caseous lesions in the teen-age group. Then there was that large army of thoracoplasty failures who needed treatment.

In the vast majority of instances, resection has been used in the treatment of such complicated forms of tuberculosis where thoracoplasty has either failed or offered little chance to control the disease. However, as experience grew and results became better, it was used in preference to thoracoplasty in certain types of lesions where thoracoplasty might have been tried first. Pneumonectomy was performed in this series of 92 resections in preference to extensive thoracoplasty in 17 instances; lobectomy in preference to thoracoplasty in 8 cases; and lobectomy in preference to revisional thoracoplasty in 2 cases. In our opinion, the remaining 65 patients could have had no therapy other than resection with any chance of success.

The type of case in which resection is indicated is a controversial subject at the present time. The question that is foremost in the minds of most clinicians is just where pulmonary resection fits into the entire scheme of treatment. This will vary from clinic to clinic but, in general, it should be used to supplement, not to compete with the other established methods of treatment. A simple rule to follow is to use it only in those cases where a high percentage of failures with other methods have occurred.

With reference to the list of indications presented in this paper, most thoracic surgeons are in agreement with the following which represents 38 of the 92 resections:

(*1*) Associated suppurative disease.
(*2*) Thoracoplasty failure.
(*3*) Basal disease that has failed to respond to all conservative measures.
(*4*) Tuberculoma.

We feel sure that most clinicans would agree that resection was indicated in the majority of patients classified as having extensive unilateral disease. Undoubtedly some surgeons would perform extensive thoracoplasty in a certain number of these cases as pointed out above. This decision is based upon an honest difference of opinion as to which form of therapy offers the best chance of cure.

The most controversial point has been the use of upper lobectomy in cases

where thoracoplasty might have been successful. We now feel that thoracoplasty should always be performed first provided the lesion is suitable. The high incidence of ipsolateral exacerbation following lobectomy has made us more cautious in using it as an elective procedure.

This brings us to the question of when resection should be used as preferred treatment. With our present experience, resection is considered the *treatment of choice* in the following:

(1) Those with associated suppuration.
(2) Unilateral disease that has failed to respond to adequate thoracoplasty.
(3) Tuberculoma.
(4) Extensive basal tuberculosis where other simpler measures have failed or are contraindicated.
(5) In preference to thoracoplasty in cases with active parenchymal disease complicated by bronchial stenosis.
(6) Progressive unilobar or unilateral tuberculosis in the teen-age group where pneumothorax is impossible or has failed.
(7) In preference to cavernostomy in the treatment of tension cavities in unilobar or extensive unilateral disease.
(8) In certain cases with extensive unilobar disease with dense opacities and little evidence of fibrosis and retraction.
(9) Nonexpandable lung following pneumothorax with extensive parenchymal disease and with or without a complicating tuberculous bronchitis.

The results following pneumonectomy have been more gratifying than those following lobectomy. When the number of desperate risks and the extensiveness of disease in those patients treated with pneumonectomy are considered, it is not so surprising to find 41 per cent of them dead two to twelve years following operation as it is to find 41 per cent of them clinically well with a negative sputum.

The disappointing results following lobectomy have been due largely to the high incidence of ipsolateral exacerbation. We should like to reëmphasize that poor judgment in applying the procedure, not the procedure itself, is probably the outstanding cause of this complication. During the past two years, more careful evaluation of the amount and type of disease in other lobes and the more routine use of post-lobectomy thoracoplasty has eliminated this complication during the postoperative period. It has occurred in only 2 cases. However, a follow-up period of several years will be required before final evaluation can be made of the problem of ipsolateral exacerbation in this group of patients. The future place of lobectomy in treating pulmonary tuberculosis will depend largely upon how much we can reduce the incidence of this complication.

Adequate care of the patient following resection is of great importance in securing good end-results. We feel that the following three factors warrant special emphasis:

(1) Prevention of overdistention of the remaining pulmonary tissue.
(2) Periodic bronchoscopic observation.
(3) Strict adherence to the fundamental principles of treating tuberculosis, especially strict bed-rest.

We are convinced that it is essential to reduce the volume of the thoracic cage following resection to prevent overdistention of the remaining pulmonary tissue. Relaxation of lung tissue is one of the basic principles in treating any tuberculous lesion. Not only does this prevent the development of emphysema, but it protects remaining tuberculous foci against reactivation. Following pneumonectomy, thoracoplasty must be sufficiently extensive to prevent mediastinal displacement. Following upper lobectomy, the aim of thoracoplasty is to reduce the remaining lobe or lobes to approximately normal volume. Here, the extent of thoracoplasty will depend upon the volume of pulmonary tissue resected. In the past, we have relied upon phrenic paralysis following lower lobectomy but we have found that it gives little or no protection. It may be that upper thoracoplasty should be utilized here, also.

Ulceration of the bronchial stump has occurred both early and late following resection. Therefore, bronchoscopic examination is advised, routinely, six weeks following operation. If this is negative, reëxamination in six months is advocated. Persistence or recurrence of positive sputum without evident parenchymal source is an indication for bronchoscopy. If ulceration is found, treatment with 30 per cent silver nitrate is recommended, at two-week intervals. Stump ulceration may result in spread of infection to the parenchyma.

We have always recognized the fact that it is impossible to excise all tuberculous foci. Because of this, strict bed-rest has been recommended for a period of at least six months following sputum conversion.

SUMMARY

1. An analysis of 88 patients (92 resections) with pulmonary tuberculosis treated by pulmonary resection between 1934 and March 31, 1944 has been presented.

2. A brief summary of results during the past two years has also been given. During this time, local anesthesia and the face-down position of the patient during operation have been used.

3. Improved operative technique has reduced the serious complications following resection and made pulmonary resection safer.

4. Ipsolateral exacerbation of remaining tuberculous foci has been the most common cause of lobectomy failure. The factors producing this complication have been analyzed. The rôle of post-lobectomy thoracoplasty in its prevention has been emphasized.

5. The operative fatality, at present, for both lobectomy and pneumonectomy is approximately 5 per cent for patients who are reasonable risks. In the desperate risk group, the operative fatality is 43.8 per cent.

6. Of the patients followed from two to twelve years, 42.4 per cent of the lobectomy series and 48.1 per cent of the pneumonectomy series are clinically well with negative sputum; 18.2 per cent of those treated with lobectomy and 41.2 per cent of those treated with pneumonectomy are dead.

SUMARIO

1. Preséntase un análisis de 88 enfermos de tuberculosis pulmonar en que se verificó la resección pulmonar entre 1934 y marzo 31 de 1944.

2. Preséntase también un breve sumario de los resultados de los dos últimos años, durante cuyo período se han utilizado la anestesia local y la posición cara-abajo del enfermo durante la operación.

3. La técnica operatoria perfeccionada ha mermado las complicaciones graves consecutivas a la resección y el peligro que ésta entraña.

4. La exacerbación ipsolateral de los focos tuberculosos restantes ha sido la causa más habitual de los fracasos de la lobectomía. Analízanse los factores que provocan esta complicación y recálcase el papel que corresponde a la toracoplastía post-lobectómica en la prevención de la misma.

5. La actual mortalidad operatoria tanto para la lobectomía como la neumonectomía representa aproximadamente 5 por ciento en los enfermos que constituyen riesgos razonables, subiendo a 43.8 por ciènto en el grupo de riesgos considerables.

6. De los enfermos observados durante dos a doce años, 42.4 por ciento de la serie lobectomizada y 48.1 por ciento de los neumonectomizados se encuentran clínicamente bien con esputo negativo, en tanto que 18.2 por ciento de los lobectomizados y 41.2 por ciento de los neumonectomizados han muerto.

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DISCUSSION

Dr. Herbert C. Maier, New York, New York: On analysis of the details presented in the paper on pulmonary resection for tuberculosis by Doctor Overholt and his associates, I find a close similarity to the results obtained by Doctor Sweet. In both clinics the experiences are similar to my own, especially in regard to the late results. Two years ago when this subject was discussed before the American Trudeau Society and encouraging early results were reported, it was appreciated that insufficient time had elapsed to permit more than a very tentative opinion concerning the final position of pulmonary resection in the treatment of tuberculosis. Even to-day it is too early to do more than present and analyze the experience gained to date. The accumulated evidence suggests:

(*1*) The late result of lobectomy and pneumonectomy in tuberculosis is influenced more by the patient's immunological reaction than by other factors. Many patients with an unfavorable reaction to their tuberculous infection, who had an early dramatic result following pulmonary resection, have since had progression of the disease. Excision of most of the tuberculous pulmonary tissue does not greatly alter the patient's reaction to his residual foci.

(*2*) Following upper lobe lobectomy there is a relatively high incidence of late exacerba-

tion of the tuberculosis on the same side. This is chiefly due to the frequency of tuberculous involvement in the apex of the lower lobe. In my own experience with thoracoplasty cases in which only four or five ribs were removed, further surgery has also often been required later because of the failure to collapse adequately the apex of the lower lobe at the original operation. Although from a functional standpoint alone upper-lobe lobectomy gives a better result than thoracoplasty (as shown by Cournand and his associates), this fact is outweighed by the consideration just mentioned.

(*3*) I believe lobectomy and pneumonectomy should be restricted to those cases in which thoracoplasty either has failed or is very likely to fail.

(*4*) A partial thoracoplasty seems advisable in most cases after upper-lobe lobectomy and after pneumonectomy.

(*5*) An analysis of the various types of cases in relation to the results one or more years after operation suggests the following tentative conclusions:

Cases of pulmonary tuberculosis with secondary pyogenic suppuration may give good late results, especially if preoperatively the tuberculous process has become more quiescent as the symptoms of secondary suppuration have increased. For this group of patients pulmonary resection has given us a new weapon.

Pneumonectomy performed for thoracoplasty failures has resulted in a higher immediate mortality, but the late results have been relatively satisfactory. The better late result in this group is probably due to the fact that the thoracoplasty failures who had the most unstable type of tuberculosis and tended to spread early to the contralateral lung never become candidates for pneumonectomy.

Patients in whom a pneumonectomy was performed for extensive unilateral tuberculosis or "destroyed lung" have had a poor late result. Many of these patients have shown progression of their contralateral disease within a few years after pneumonectomy. The "destroyed lung" indicates poor resistance to tuberculosis which is not fundamentally altered by pneumonectomy. I believe thoracoplasty is preferable to pneumonectomy in this group in the absence of secondary pyogenic suppuration.

The late results of lobectomy for lower-lobe lesions in which the indications were well chosen have been relatively good.

(*6*) Although the face-down position of the patient during operation, as suggested by Doctor Overholt, may lessen the risk of contralateral spread during operation, it does not alter the late exacerbations which are numerically far more important. I have operated on some tuberculous patients through an anterior approach in order to avoid the gravitation of secretions into the opposite lung.

OLEOTHORAX[1]

JOHN H. MOYER, JR.[2]

Oleothorax as a treatment for pulmonary tuberculosis was first introduced in France by Bernou in 1921. The first extensive report in this country was made in 1932 by Matson (1). However, to date, the literature on oleothorax is comparatively scant, especially follow-up reports, such as this one.

Oleothorax has been discarded by many clinics in this country because its value has often been questioned. I do not present these findings as a champion of oleothorax or with the belief that it should be a substitute for good chest surgery. I do not think it should!

This study is based on 91 cases treated at the Belmont Hospital from 1932 to 1939, inclusive. From this series, as well as from similar reports by others (1, 2, 3, 4, 5, 6), we feel there is a definite group of patients, although a small one, which should receive the benefits of oleothorax.

INDICATIONS

The indications, as set forth at this hospital by Baker (4) when oleothorax therapy was first instituted, were:

(*1*) As an "inhibition oleothorax" to inhibit expansion of the lung in patients in whom a previously satisfactory artificial pneumothorax threatens to be lost. The following contraindications should not exist:
- (a) Actively progressing disease in the collapsed lung.
- (b) Thin-walled cavities near the pleura.
- (c) Adhesions traversing the pneumothorax space.
- (d) Bronchopleural fistula.

(*2*) As disinfection treatment for tuberculous empyema when the following contraindications did not exist:
- (a) Bronchopleural fistula.
- (b) Pleurocutaneous fistula.
- (c) Advancing disease. This last contraindication was discarded if toxemia was progressive and if parenchymal lesions were not markedly malignant. Moreover, this contraindication was waived if oleothorax was thought imperative to control the disease.

(*3*) As a compression oleothorax. (This was soon abandoned because of unsatisfactory reports.) (3)

TECHNIQUE

In cases of obliterative pleuritis 20 cc. of olive oil or mineral oil were injected to test the sensitivity of the pleura. If no reaction occurred within one week,

[1] The information presented in this paper was collected and arranged from material at the Belmont Hospital, Worcester, Massachusetts, with the assistance of Arthur D. Ward, M.D., Medical Director; U. E. Zambarano, M.D., Consultant in Tuberculosis; and Louise Bacastow, Medical Secretary.

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oleothorax therapy was started. At one sitting an average of 200 cc. of oil was given, preceded by the removal of an equal amount of air. Intrapleural pressures were always checked and adjusted to near zero before the patient was returned to the ward. Oil was administered once a week until the pleural space was filled.

In cases of empyema practically the same procedure was followed except that fluid instead of air was aspirated, and 5.0 per cent gomenol in oil was used. Pleural sensitivity was first tested with 20 cc. of oil, followed by weekly injections of 200 to 400 cc. This was continued until the empyema was arrested or until the pleural space was filled with oil. When the desired amount had been given, fluid alone was removed from beneath the oil until it no longer formed. Total amounts of oil injected varied from 300 to 3,750 cc. Markedly positive pressures were carefully avoided. Fluoroscopic examinations and X-ray films were made as indicated. Oil was maintained here, as well as when used as an inhibition oleothorax, as a more or less permanent measure. It was only removed if, for one reason or another, it proved unsatisfactory.

RESULTS IN 84 PATIENTS WITH TUBERCULOUS EMPYEMA TREATED WITH OLEOTHORAX

The duration of disease before oleothorax was instituted varied from six months to fourteen years as determined from history and X-ray examinations. The average duration was about five years.

When therapy was started, 79 had caseous and 5 fibrocaseous tuberculosis. Fifty-nine (70 per cent) had bilateral parenchymal involvement. Forty-five (77 per cent) of the 58 living cases and 17 (66 per cent) of the 26 fatal cases had cavities at the onset of therapy. It is interesting that, of the entire series of 84 patients with empyema, 44 occurred during pneumothorax therapy, 36 followed pneumonolysis and only 4 were not associated with collapse therapy.

Analysis of the living patients: (Table 2.) Of the total of 84 cases at the outset of treatment, 54 (64 per cent) showed good early results (one to three years after the beginning of treatment). However, 26 (31 per cent) are now dead; 58 (69 per cent) are living, of which 45 (54 per cent) are apparently cured, 2 (2 per cent) arrested and 11 (13 per cent) remain active.

By comparing tables 1 and 2 we can see that, of the 54 cases of far advanced disease at the beginning of therapy, 33 are still living, of which 3 have been followed at least ten years and 30 have been followed for at least five years. Of the 27 moderately advanced cases when oleothorax was instituted, 22 are still living, of which 3 have been followed ten years and 19 have been followed five years. All 3 minimal cases are still living after five years. The "ten-year" follow-up periods varied between ten and twelve years with an average of ten years and six months since the administration of oil. The "five-year" follow-up periods varied between five and nine years with an average of seven years. We should also note that the prognosis for cure in the moderately advanced group was nearly twice as good as that of the far advanced group, that is, 19 (71 per cent) of the original 27 patients with moderately advanced disease are

now classified as apparently cured, as compared to 24 (44 per cent) of the original 54 patients with far advanced disease. Two per cent of the patients with moderately advanced disease are considered only arrested because they have

TABLE 1

Extent of disease according to age groups before treatment in 84 patients

AGE GROUPS	FAR ADVANCED		MODERATELY ADVANCED		MINIMAL		TOTAL	
	Number of cases	Per cent of total cases	Number of cases	Per cent of total cases	Number of cases	Per cent of total cases	Number of cases	Per cent of total cases
15–30	41	49	19	23	3	3	63	75
30–40	9	11	7	8	—	—	16	19
Over 40	4	5	1	1	—	—	5	6
Total.....	54	65	27	32	3	3	84	100

TABLE 2

Present status of the 58 living patients

STATUS AND CLASSIFICATION	FAR ADVANCED		MODERATELY ADVANCED		MINIMAL	TOTAL	PER CENT OF LIVING PATIENTS	PER CENT OF ENTIRE SERIES
	After 10 years	After 5 years	After 10 years	After 5 years	After 5 years			
Number of living cases.....	3	30	3	19	3	58	100	69
a. Sputum								
Positive.....	—	3	1	1	—	5	9	—
Negative.....	3	27	2	18	3	53	91	—
b. General condition								
Good.....	3	22	2	19	2	48	83	—
Fair.....	—	4	1	—	1	6	10	—
Poor.....	—	4	—	—	—	4	7	—
c. Clinical classification at present								
Active								
Minimal B.....	—	—	—	—	—	—	—	—
C.....	—	—	—	—	—	—	—	—
Moderately advanced B	—	—	—	—	1	1		
C	—	—	—	—	—	—		
Far advanced B.....	1	1	—	—	—	2	19	13
C.....	—	5	1	—	—	6		
D.....	—	2	—	—	—	2		
Arrested.....	—	—	1	1	—	2	3	2
Apparently cured.....	2	22	1	18	2	45	78	54

not been followed long enough since their disease became arrested to be classified as apparently cured.

Case Reports

1. *Ten-year follow-up on patients with far advanced disease:*

A. Apparently cured: Two patients are free of symptoms and in full-time employment. One of these developed bronchopleural and pleurocutaneous fistulae soon after oleothorax was instituted. These closed spontaneously after several months and recovery was uneventful.

B. One patient, classified far advanced B, is a 30 year old male who received, 2,700 cc. of oil ten years previously. The empyema failed to become arrested and the oil and fluid were aspirated, following which the process subsided. However, after nine years he has developed contralateral disease.

2. *Five-year follow-up on patients with far advanced disease:*

A. Twenty-two patients are apparently cured and lead normal lives. Included here are: one male who had a bronchopleural fistula before oleothorax which closed spontaneously; one with tuberculosis of the kidney which cleared spontaneously; 2 with rectal fistulae which closed spontaneously. On 2 patients, because of failure of oleothorax to arrest the empyema, drainage and thoracoplasty had to be done.

B. One patient, classified far advanced B, is a 28 year old female in whom a previously existing cavity has opened again under the oil. Drainage and thoracoplasty are advised.

C. Five patients are classified far advanced C. The prognosis of all of these is poor. Included here are: a 38 year old male who recently developed a bronchopleural fistula for which drainage and thoracoplasty have been done; and a 32 year old female who developed contralateral disease. Aspiration of oil with reëxpansion was attempted unsuccessfully on the latter; contralateral pneumothorax was also attempted and was unsuccessful.

D. Two patients are classified far advanced D; in them prognosis is hopeless. One of these received additional drainage and thoracoplasty which likewise failed.

3. *Ten-year follow-up on patients with moderately advanced disease:*

A. One of these patients is apparently cured.

B. One, a 34 year old female, is now apparently arrested; she received drainage, a modified Schede operation and thoracoplasty because of bronchopleural and pleurocutaneous fistulae.

C. One patient is now classified far advanced C; she is a 34 year old female, who developed contralateral tuberculosis and hemorrhage.

4. *Five-year follow-up on patients with moderately advanced disease:*

A. Eighteen patients are apparently cured. Included here is one of the patients who also received additional drainage and thoracoplasty because of a small bronchopleural fistula.

B. One patient is classified as apparently arrested because he has not been followed long enough to be classed as apparently cured.

5. *Minimal cases:*

A. Two patients are apparently cured.

B. One patient is classed as moderately advanced B because of recent symptoms and X-ray evidence of a bronchopleural fistula; drainage and thoracoplasty have been advised.

Analysis of dead patients: The mortality was by far the highest in the far advanced group, 21 (39 per cent) of the 54 patients, as compared to 5 (18 per cent) of the 27 patients in the moderately advanced group. There were no fatal cases in the minimal group. Thus, 81 per cent of the total mortality occurred within the group of far advanced patients. One would expect this merely from the natural course of the disease.

The fatal cases lived for an average of one year and nine months. None died after four years and three months, suggesting that many of the early fatalities were due to the very poor condition of the patients at the start of treatment. No patient was denied therapy if his immediate prognosis was not hopeless, regardless of his ultimate prognosis.

TABLE 3

Analysis of mortality

CAUSE OF DEATH	FAR ADVANCED	MODERATELY ADVANCED
	Number of cases	
Spread of disease (pregnancy)	—	1
Bilateral spread and spontaneous pneumothorax	1	—
Bilateral spread with hemorrhage	2	—
Bilateral spread alone	8	3
Bilateral spread with bronchopneumonia	—	1
Bilateral spread with contralateral empyema	1	—
Bilateral and hematogenous spread	2	—
Bilateral spread and bronchopleural fistula	5	—
Bilateral spread with hemorrhage and pleurocutaneous fistula (present before oleothorax)	2	—
Total	21	5
Percentage of entire series (84 cases)	25 per cent	6 per cent

It is apparent that in practically every patient who died spread of disease was the immediate cause of death (table 3). If another complication existed, it was always accompanied by spread of disease, so that we cannot be sure that the complication was not unrelated to the cause of death in most cases.

Six dead patients had complications associated with oleothorax therapy, that is, 5 cases with bronchopleural fistulae and one case with spontaneous pneumothorax. The bronchopleural fistulae may have been present before oil was administered and may have been the cause of empyema, as they all became apparent soon after oil was first given; they were progressive until death. In the 2 cases with pleurocutaneous fistulae, these were present before oil was given and cannot, therefore, be attributed to oleothorax. The patient with pregnancy was discharged with negative sputum and apparently arrested disease. She immediately became pregnant and died from spread of the disease in the seventh month of pregnancy. The case with contralateral empyema developed active disease on the contralateral side at the time that oil was given on the ipsolateral

side, death following in three months. Oil was *not* administered on the contralateral side.

Because of failure to arrest empyema, 3 of these cases, including one with bronchopleural fistula, one with hematogenous spread and one with bilateral spread and spontaneous pneumothorax, received, in addition, rib resection and drainage without avail.

Complications: As shown in table 4, 11 (13 per cent) patients developed complications either concomitant with, or attributable to oil. Six of these received no further treatment and 4 have subsequently died, one remains morbid and one

TABLE 4

Number of complications with oleothorax—living and dead patients

	NUMBER OF CASES WITH COMPLICATIONS							
	BRONCHOPLEURAL FISTULA		BRONCHOPLEURAL AND PLEUROCUTANEOUS FISTULA		SPREAD AND SPONTANEOUS PNEUMOTHORAX		TOTAL	
	Number of cases	Per cent	Number of cases	Per cent	Number of cases	Per cent	Number of cases	Per cent
Far advanced	6	—	1	—	1	—	8	—
Moderately advanced	1	—	1	—	—	—	2	—
Minimal	1	—	—	—	—	—	1	—
Total	8	10	2	2	1	1	11	13
Additional therapy and final results:								
Needing additional surgery	3	—	1	—	1	—	5	—
Apparently cured with surgery	1	—	—	—	—	—	1	—
Arrested following surgery	—	—	1	—	—	—	1	—
Morbid at present	2	—	—	—	—	—	2	—
Spontaneous cure	—	—	1	—	—	—	1	—
Dead	5	—	—	—	1	—	6	—

Note: In addition to these complications, there were 4 (5 per cent) patients in whom oleothorax failed to arrest the empyema. They received rib resection, drainage and thoracoplasty. Subsequently, one has died, 2 are apparently cured and one remains morbid at this time and is classed far advanced D.

had a spontaneous cure. Five received additional surgery, that is, drainage and thoracoplasty. Of this group, 2 died, one remains morbid, one is apparently cured and one is arrested. These latter 2 patients, as well as the 2 patients who apparently became cured following surgery in which the oleothorax alone failed to arrest the empyema, will be deducted from our final results. Thus, in referring to table 2, we see that, of the 84 original patients, 45 are apparently cured and 2 are arrested. If we deduct the 3 cases, apparently cured and one case arrested with additional surgery, we have left 42 (50 per cent) apparently cured and one (1 per cent) arrested with oleothorax alone. This allows us a total of 51 per cent satisfactory long-term results. In further discussion, these latter figures will be the ones to which we refer.

RESULTS IN 7 PATIENTS WITH OBLITERATIVE PLEURITIS TREATED WITH OLEOTHORAX

The 7 cases of obliterative pleuritis are not a large enough group from which to draw any conclusions, but they are added to the series since few patients who received oleothorax for this indication are reported in the literature. The number of patients at this hospital is especially low because the staff was quite reluctant to use this indication when oleothorax was first used, but have since used it more freely. However, the period of observation since administration of oil in these more recent cases has not been long enough to report them at this time. Perhaps the largest series for this indication is that of Browning, Dundon and Ray (2) who report 53 cases.

Five of the 7 patients fell in the age-group of 15 to 30 and 2 in that of 30 to 40 with an average age of 28 years. All have received oil five or more years ago with an average of eight years. Two cases had positive sputa as well as previous X-ray evidence of cavities which had closed and 5 had negative sputa without cavities before the institution of oleothorax. There were no adhesions traversing the pleural space. Three cases were far advanced and 4 were moderately advanced at the beginning of therapy. All had caseous lesions. The amount of oil given ranged between 650 and 1,000 cc., with an average of 780 cc.

Other therapeutic measures included 4 who received pneumothorax and pneumonolysis, 2 who received pneumothorax and phrenic crushing and one who received pneumothorax alone.

Following oleothorax administration, there were no complications directly attributable to the oil. One case died and 6 (86 per cent) are apparently cured after five years.

The one patient who died had far advanced disease, apparently arrested at the time of discharge. She was readmitted two years later, four years after oleothorax was started, with bilateral spread of disease which rapidly progressed until death. She had no other complications and was one of the 5 patients in whom neither a cavity nor positive sputum was demonstrated before therapy.

Of the 6 living patients (2 far advanced and 4 moderately advanced), all have negative sputa at present and are classed as apparently cured; they lead a normal life as regular employees doing various forms of suitable work. The oil has been left in the chest in all of these cases. The patients are fluoroscoped and X-rayed every four months. There have been no complications in this group.

The oil is particularly satisfactory in these cases because it maintains collapse over the diseased area in contrast to oleothorax for empyema. In obliterative pleuritis the adhesions usually begin at the base and work up to the apex so that by the time oil is given a walled-off space over the apex is present. Therefore, the oil when given is held at the apex maintaining a selective collapse over the diseased area.

From our results as well as those of others, it would appear that progressive obliterative pleuritis is the cardinal indication for oleothorax if there is a ten-

dency toward active disease, should collapse be lost. The only other alternative is reëxpansion, followed by thoracoplasty.

In general, well known authorities (1, 2, 5, 6, 7, 8) using this therapeutic measure followed somewhat the same procedure and contraindications as we have. If anything, there has been a definite conservative swing including Howlett (6) who is of the opinion that, in addition to the contraindications mentioned earlier in the paper, parenchymal disease should be satisfactorily controlled with cavities closed and negative sputa. If, however, this state of affairs *has existed long enough* to make pulmonary expansion feasible, even though the duration of collapse is not optimal, this should be chosen in preference to oleothorax.

If the above criteria are followed, there will probably be no more than 4 or 5 patients per year in a sanatorium of 100 to 150 beds. It is estimated by Hetherington (7) of Henry Phipps Institute of Philadelphia that approximately 5 per cent of their patients with successful pneumothorax maintained longer than six months receive oleothorax because of threatened pleural symphysis.

OLEOTHORAX IN TREATMENT OF EMPYEMA

Oleothorax in the treatment of empyema is by far a more controversial subject than is oleothorax for obliterative pleuritis. This has largely been replaced by rib resection, drainage and thoracoplasty. However, we feel that it should be kept in mind as an important alternative if, for one reason or another, surgery is not possible, that is, should a patient refuse surgery, etc.

In the use of oleothorax for the treatment of empyema, Hayes (9) of Saranac Lake suggests that, in addition to the previously mentioned contraindication, "The lungs should be under control (cavity closed, negative sputa) and a fair trial of aspiration and lavage first used. If these criteria are not filled, surgery is preferred unless surgical collapse is contraindicated by active disease in the opposite lung."

Not only are the indications for oleothorax in empyema controversial, but the length of time it should be maintained, as well. Although oleothorax is used as a permanent measure in this clinic, it is the impression of Cournand (10) and substantiated by Kaufman (11) that "Oleothorax should be viewed as a temporary measure. It is not desirable to maintain oil in the thorax permanently unless frequent checks on the pressure are made."

It is known that, should oleothorax be maintained for long periods of time (five to eight years), the collapsed lung will not reëxpand. This has been shown by 6 patients in whom we attempted to reëxpand a collapsed lung, having maintained oleothorax for over five years. We were 100 per cent unsuccessful. It has also been shown, in 11 autopsies performed on oleothorax patients in this hospital, that the oil was well encapsulated and the pleura markedly thickened, although the oil was clear and there was no evidence of infection. This has also been observed by Herbert and Charr (12).

At first glance, 50 per cent apparently cured and one per cent arrested, or a total of 51 per cent good late results with oleothorax alone, seem extremely low in comparison to various reports on thoracoplasty. However, it must be kept in

mind that these patients were not carefully selected, which is not true of patients receiving thoracoplasty. Alexander (13) reports a series of thoracoplasties with 74.4 per cent cured, 9.3 per cent living and 16.3 per cent dead in selected patients over a six-year period. On the other hand, when all the patients with empyema, admitted to the surgical service at the University of Michigan during the same period and receiving various treatments including thoracoplasty, are reviewed, only 54.3 per cent are apparently cured, 12.8 per cent are living but morbid and 32.9 per cent are dead. These latter figures are not much different from our series of 50 per cent apparently cured, one per cent arrested, 13 per cent morbid and 31 per cent dead, especially since all our cases are reported with no less than five years of observation.

Results of thoracoplasty by well-known thoracic surgeons parallel those of Alexander, as for example, Overholt (14) who reports 80 per cent and Hedblom (15) 78 per cent cured.

In comparing our figures of oleothorax with Matson's (1) series of oleothorax in the treatment of empyema, we obtained approximately the same results, that is, 60 per cent satisfactory early results of Matson as compared to 64 per cent good early results in our patients. Matson has not reported figures comparable to our late results. In his series of 50 patients, 4 developed pleurocutaneous fistulae, 4 developed bronchopleural fistulae, or a total of 15 per cent developed complications due to oleothorax; in 4 patients (8 per cent) oleothorax failed to arrest the empyema. This compares to 10 per cent of patients in our series who developed bronchopleural fistulae, 2 per cent who developed bronchopleural and pleurocutaneous fistulae and one per cent spontaneous pneumothorax, or a total of about 13 per cent with complications related to oleothorax, plus 5 per cent in whom oleothorax failed to arrest the empyema.

Browning, Dundon and Ray (2) report a series of 68 per cent satisfactory results in follow-up periods ranging from one to seven years. However, their cases were more carefully selected and did not receive oleothorax in the presence of marked systemic symptoms or in the presence of rapid fluid formation. This seems to indicate that, if cases are selected as are the cases for surgery, good results can be expected. Therefore, in conclusion it would seem that thoracoplasty, plus additional surgery, is the method of choice in the treatment of tuberculous empyema, but that oleothorax should be kept in mind as an important alternative method, should we not be able to use surgery for one reason or another.

SUMMARY AND CONCLUSIONS

1. Eighty-four cases of tuberculous empyema and 7 cases of obliterative pleuritis were treated with oleothorax.

2. The incidence of empyema as a complication of pulmonary tuberculosis is proportional to the severity of the disease.

3. Five years after receiving oleothorax for empyema, 54 per cent are apparently cured, of which 4 per cent received additional surgery. Two per cent are arrested, of which one per cent received additional surgery. Thirteen

per cent remain active and 31 per cent are dead. Therefore, 51 per cent satisfactory late results, that is, five years or more, can be claimed for this series.

4. A "five-year" cure was observed in 71 per cent of moderately advanced cases; this was nearly twice as good as for the far advanced cases (44 per cent).

5. Eleven (13 per cent) of the 84 patients with empyema developed complications attributable to oil, that is, bronchopleural or bronchopleural and pleurocutaneous fistulae or spontaneous pneumothorax, 6 of whom died. Four cases (5 per cent) failed to become arrested with oleothorax therapy alone.

6. Of the 7 cases receiving oleothorax for obliterative pleuritis, one died from spread of disease and 6 are classified as apparently cured at the five-year follow-up.

SUMARIO Y CONCLUSIONES

1. Ochenta y cuatro casos de empiema tuberculoso y 7 casos de pleuritis obliterante fueron tratados con oleotórax.

2. La incidencia del empiema como complicación de la tuberculosis guarda proporción con la gravedad de la enfermedad.

3. A los 5 años de recibir el oleotórax por empiema 54 por ciento de los enfermos se hallan aparentemente curados, habiendo sido objeto 4 por ciento de ellos, de otras intervenciones quirúrgicas. Dos por ciento se hallan estacionados, con otras medidas cruentas en 1 por ciento de ellos. Trece por ciento continúan siendo activos y 31 por ciento han muerto. Es, pues, evidente que en esta serie de 84 casos de empiema tuberculoso obtúvose en 51 por ciento un resultado satisfactorio prolongado (de cinco años o más) con un tratamiento a base exclusiva de oleotórax.

4. La proporción de curaciones de cinco años (41 por ciento) en los casos moderadamente avanzados fué casi tan buena como en los muy avanzados (44 por ciento).

5. Once (13 por ciento) de los 84 casos de empiema manifestaron complicaciones imputables al aceite: fístulas broncopleurales o broncopleurales y pleurocutáneas, o neumotórax espontáneo, falleciendo seis de los enfermos. En cuatro casos (5 por ciento) no se estacionó la enfermedad con la oleotoracoterapia sola.

6. De los 7 casos de pleuritis obliterante que recibieron el oleotórax, uno falleció de difusión de la enfermedad y los otros 6 se consideran como aparentemente curados al cumplirse el período se observación de cinco años.

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BCG VACCINATION IN SCANDINAVIA[1]

Twenty Years of Uninterrupted Vaccination against Tuberculosis

KONRAD BIRKHAUG[2, 3]

BCG vaccination of a rapidly increasing population of negative tuberculin reactors, intimately exposed to tuberculous infection, has become an established public health measure in Norway, Sweden and Denmark since 1926. This interest in BCG vaccination has in no way been allowed to interfere with established antituberculosis measures, such as tuberculin surveys and mass X-ray examinations for detection of tuberculous disease and controlled isolation and treatment of open cases of tuberculosis, in order to prevent the dissemination of tubercle bacilli. These vigilant measures have resulted in reducing the tuberculosis mortality in Scandinavia from more than 250 per 100,000 population in 1900 to less than 70 in 1944. A proportional decrease in tuberculosis morbidity, however, has not been observed.

During the past forty years a remarkable shift has been observed in Scandinavia in the age-period when the primary tuberculous infection takes place. At the turn of the century, about 50 per cent of persons were tuberculin reactors between 10 and 15 years of age and almost 90 per cent between 25 to 30 years. In 1944 only 20 per cent of the former and 50 per cent of the latter age groups had had contact with tubercle bacilli and the peak of tuberculous disease was observed in the 20 to 30 age group.

Scandinavian clinicians have likewise observed that the acute and rapidly fatal exudative type of tuberculosis has become unexpectedly common among adolescents and young adults who did not react to tuberculin. They believe that the best hope for controlling this advanced shift in the time of primary tuberculous infection lies in BCG vaccination. The basis for this belief is (*a*) the absolute harmlessness of the BCG vaccine both in animals and in man, and (*b*) its ability to produce a mild tuberculin reactivity and a relatively high protection against an exogenous infection with virulent tubercle bacilli. These widely accepted facts have completely disarmed the Scandinavian opposition to the use of a vaccine consisting of living tubercle bacilli of attenuated virulence, inasmuch as the preferable use of heat-killed or chemically-killed tubercle bacilli for immunization unfortunately has fallen short of the desired results.

The immunizing effect of the living *Bacille Calmette-Guérin*, commonly called BCG, has been exhaustively studied in animals and man. The results of these universal investigations establish BCG as a perfectly harmless and very effective

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vaccine which stimulates a relatively high degree of resistance against a virulent infection with tubercle bacilli. The data on BCG have most recently been prepared by Professor W. H. Tytler (1) as a memorandum for a joint committee of the Tuberculosis Association, the Joint Tuberculosis Council and the National Association for the Prevention of Tuberculosis in Great Britain, for the consideration of the Ministry of Health. This memorandum presents an overwhelming case in favor of BCG. Incidentally, it pays tribute to the Scandinavian "classic basis for an application of BCG."

The average duration of tuberculin sensitiveness which results from BCG vaccination is in excess of four years, although in some cases it terminates after one year. The main drawback of the intracutaneous mode of vaccination, namely local abscesses and protracted healing, has been completely eliminated by transcutaneous vaccination. It should be mentioned, however, that the intracutaneous method performed by experts very seldom leads to abscess formation.

For these cogent reasons, BCG vaccination has been taken up by the National Tuberculosis Associations in Norway, Sweden and Denmark, on a steadily increasing scale since 1926, until it has become an integral part of their prophylactic defense program against tuberculous disease. The purpose of this address is to present a review of the past twenty years' experiences with BCG vaccination in Scandinavia.

BCG VACCINATION IN NORWAY

Although BCG vaccination has been done sporadically in Norway since 1924 by private physicians and especially in children intimately exposed to tuberculous infection in their homes, no controlled BCG investigation was attempted before the well known studies by Heimbeck (2) on student nurses at the Ullevål Communal Hospital in Oslo, and on medical students by the late Scheel (3) at the University in Oslo.

In January, 1924 Heimbeck set out to investigate the frequency of tuberculous disease among student nurses who had entered either as negative or positive tuberculin reactors. During their three-years' training, part of which was served on open tuberculosis wards, these student nurses formed a particularly suitable group for a controlled study preparatory to BCG vaccination of the negative tuberculin reactors. They formed at the same time a class in much greater need of protection against tuberculosis than the population as a whole. On the basis of these tuberculin reactors, Heimbeck made the now universally recognized observation that those who are negative reactors on entry more often contract clinical tuberculosis during their three-years' hospital training than those who are originally positive reactors. Thus he found only 0.9 per cent tuberculosis and no deaths from it among 625 tuberculin reactors on entry, whereas 22.4 per cent tuberculosis and 3.6 per cent deaths from it occurred among 280 who were tuberculin-negative on entry.

This important epidemiological observation was shortly afterwards confirmed by Tørnell (4) among student nurses at the Red Cross Nursing Home in Stock-

holm, among whom the frequency of tuberculosis was 0.2 per cent among 451 tuberculin reactors on entry, and 17 per cent among 108 who were tuberculin-negative on entry. Similar observations were made by Rist (5) in Paris, Israel, Hetherington and Ord (6), Brahdy (7) and Zacks and Sartwell (8) in this country, while Plunkett, Weber, Siegal and Donk (9) in the Newark School for Mental Defectives found little difference between the two groups of reactors. They observed, however, that, when reinfection takes place after the primary infection in previously negative reactors, the disease is more rapidly progressive and fatal, an observation confirmed by Scandinavian investigators.

The observations made by Heimbeck and other Continental and American investigators upset the traditional belief that adult tuberculous disease represents an extension of childhood infection. This belief was now to be replaced by a growing conviction that in the young adult it is much more commonly the result of a new infection, either in a person not previously infected or in one who has been infected in childhood and, having recovered completely, has lost all allergy and immunity in the intervening period.

These observations must not, as a matter of fact, be interpreted as a proof of an acquired specific resistance against tuberculosis, inasmuch as the tuberculin-positive group of healthy student nurses represents a chosen class of persons possessing a certain degree of natural resistance to tuberculous infection. As such they are not wholly comparable to the tuberculin-negative group of student nurses from whom persons especially susceptible to tuberculosis had not been previously eliminated. In any case, one must not claim that tuberculin sensitiveness and tuberculosis immunity are identical factors, even though they would seem to run parallel. If the tuberculin-negative student nurse could be protected against tuberculous infection in her future work, then, theoretically at least, she is better off than the tuberculin-positive student nurse who besides is exposed to a certain risk that her latent tuberculous infection may exacerbate. But, inasmuch as such protection from infection is impossible of accomplishment even in a modern hospital, one must for practical purposes aid the tuberculin-negative student nurse to acquire a specific tuberculosis immunity by means of the harmless BCG vaccine.

Thus, Heimbeck began to vaccinate intracutaneously with BCG tuberculin-negative pupil nurses, who voluntarily consented, in 1926, the nurse being isolated from tuberculous infection for about six weeks until she became tuberculin-positive. Among 287 who became positive after BCG vaccination, the annual incidence of tuberculosis was 2.6 per cent and 0.2 per cent of deaths from it, whereas, among 107 student nurses remaining negative, the incidence of tuberculosis was 17.6 per cent and 1.8 per cent mortality from it. In other words, the incidence of tuberculosis was only one-seventh among the group vaccinated with BCG.

In order to prove still further that young adult women in frequent contact with tuberculous patients are exposed to a greater risk of tuberculous infection and disease than is the young adult woman in the general population, Heimbeck showed by the same procedure that the incidence of tuberculosis among 467

tuberculin-positive females, aged 13 to 24, in the general population in Oslo was approximately 50 per cent less than among 991 tuberculin-negative females of the same age groups, and in the latter group only 1.3 per cent presented clinical tuberculosis (table 1).

Scheel found that, of those medical students at the University in Oslo who began their clinical studies as negative tuberculin reactors, 4.31 per cent contracted tuberculous disease during the medical course, whereas only 1.47 per cent of the tuberculin reactors on entry became tuberculous during the same period. If the tuberculin-negative medical students became positive following BCG vaccination, the incidence of tuberculosis fell below 2 per cent during the medical course.

TABLE 1

Incidence of all forms of tuberculosis in nurses and in the general population

GROUP	CASES	OBSERVATION	TUBERCULOSIS (PER 1,000 OBSERVATION YEARS)	
			Disease	Deaths
		years		
Nurses at Ullevål:				
Tuberculin-positive at entry	625	2,659	10.1	0
Tuberculin-negative at entry (not vaccinated)	280	561	171.0	17.8
Vaccinated BCG:				
Becoming positive	287	910	8.8	1.1
Remaining negative	107	204	107.9	9.1
Females, aged 13 to 24, general population, Oslo:				
Tuberculin-positive	467	2,111	6.6	0.5
Tuberculin-negative	991	4,697	11.1	0.6

For calculation of observation-years, tuberculin-negative persons remained classed as such to one year after showing a positive reaction, on the basis that any disease observed during that year is part of the primary infection.

Both Heimbeck and Scheel made the important observation that BCG vaccination not only protected in a high degree against the morbid sequels of the primary infection, but that also the incidence of "genuine pulmonary tuberculosis" was significantly reduced.

The favorable results of BCG vaccination reported by Heimbeck and Scheel commended themselves to the Norwegian National Tuberculosis Association, and its Board of Directors decided in 1936 to build and finance the first National BCG Laboratory in Bergen and the author became its first director. Subsequently, BCG vaccination became obligatory for all tuberculin-negative student nurses, but it was left on a voluntary basis for tuberculin-negative medical students, sanatorium and hospital personnel, conscripts in the Army and Navy, seamen and fishers aboard smaller crafts, and for all persons exposed

to tuberculous infection in localities where protection was difficult. The general antivaccination sentiment was accentuated by complaints of too frequent abscesses at the site of BCG vaccination. Such abscesses varied between 35 and 10 per cent and occurred most often when the vaccine was injected subcutaneously rather than intracutaneously. In the hands of experts the frequency of abscesses following the intracutaneous injection is reduced to about 5 per cent. By introducing the Rosenthal multiple puncture method in 1939 the handicap with abscesses was completely eliminated and two-thirds of the Norwegian vaccinating physicians took up the transcutaneous vaccination method by scarification or multiple puncture. The latter was greatly facilitated with a spring-actuated 40-needled apparatus (11) which performed the vaccination with one downward stroke.

BCG vaccination, which was lagging before 1939, was greatly activated when the cruel exigencies of the German occupation of Norway crowded large numbers of tuberculin-negative young people into small and unhygienic living and working quarters. Endemics of tuberculous disease were reported in all parts of the country and mostly among young people between 15 and 35 years of age. Segregation of open cases was far from complete and the work in tuberculosis dispensaries was greatly handicapped by military and political interference. Tuberculosis experts conferred with leading life insurance companies who generously assumed the financial responsibility for nation-wide BCG vaccination of as many as possible negative tuberculin reactors between 15 and 35 years of age. A series of popular pamphlets were distributed throughout the country to health bureaus, physicians, schools, factories, offices, etc. When the campaign became a success everywhere in the spring of 1941, the Quisling health authorities raided the health bureaus and schools in the larger cities and confiscated available BCG literature. Simultaneously they made an official decree against mass BCG vaccination as well as miniature X-ray examinations. The transparent excuse was that "the German army of occupation had brought endless medicinal supplies to Norway; the nation's health was excellent and in no instance warranted the partisan false alarm which the country's tuberculosis experts had perpetrated." The result of this ignominious interference with the nation's health was that BCG vaccination "went underground" and the number of individual vaccinations leaped from 674 in 1940 to 4,544 in 1941, 6,256 in 1942, 13,515 in 1943, 17,519 in 1944 and more than 22,500 in 1945. Inasmuch as these official figures represent only about 50 per cent of the returned reports, the actual number of BCG vaccinations during the five years of occupation lies closer to 120,000, or roughly speaking 4.8 per cent of Norway's population of about 2,500,000.

For political reasons the Quisling health authorities suppressed publication of vital statistics during the war. After capitulation it was discovered that, in spite of almost superhuman efforts to maintain the prewar uninterrupted decline in tuberculosis morbidity and mortality, both curves show slight increases during 1943 to 1945. But the increments are fortunately much lower than anticipated and the figures are not higher than for the 1930 to 1939 period.

Carefully analyzed records of BCG vaccinated persons in the two largest

cities, Oslo (250,000 population) and Bergen (120,000 population) indicate a very considerable degree of immunizing efficiency of the vaccine. The average tuberculin reactions were about 95 per cent two months after vaccination and its duration about four to five years. Statistical analysis of 12,600 persons vaccinated with BCG between 1927 and 1945 at the Oslo Municipal Tuberculosis Bureau is presented by Dahl and Hertzberg (10). In comparing the data on the vaccinated group with the tuberculosis morbidity and mortality for Oslo's general population, calculated per 1,000 per year in the age groups from birth to 50, they observe that the incidence of destructive tuberculous disease is one-tenth, nondestructive tuberculosis less than one-fourth and deaths from tuberculosis 1:5.6 among the vaccinated group as compared to the non-vaccinated general population in Oslo.

James-Olsen's and my own (11) material from the BCG Dispensary at the Bergen Municipal Health Bureau comprises almost 10,000 BCG vaccinated persons between 1937 and 1946. Rosenthal's multiple puncture method was used exclusively in this series. About 95 per cent of positive Mantoux tests with 1 mg. OT were obtained two months after vaccination and the average duration exceeds four years, although the positive reaction may become negative as soon as one year after vaccination. Follow-up examinations with annual tuberculin tests and chest X-ray films have been done in about 80 per cent of the vaccinated subjects. Up to April, 1946 no deaths from tuberculosis, 11 cases of completely healed hilar node infections, one case of exudative pleurisy and only 2 cases of progressive pulmonary tuberculosis have been found among the examined vaccinated subjects, only one-ninth as much pulmonary tuberculosis and one-sixth as much nondestructive tuberculosis as among the general population in Bergen during the same period. The tuberculosis mortality was 78 per 100,000 for the same population in 1944, while no deaths from the disease occurred among the vaccinated group.

The experience gained up to date with BCG vaccination in Norway has encouraged the National Tuberculosis Association to enact a law this year for the obligatory BCG vaccination of every negative tuberculin reactor in the eighth grades of the public schools and at the same time to encourage voluntary vaccination of every negative tuberculin reactor between 15 and 50 years of age, with reëxamination every fourth year.

Norway has already enacted laws for obligatory tuberculin tests of the entire school population, obligatory miniature X-ray examination of the entire population and obligatory control of all open cases of tuberculosis. The ultimate goal is to make BCG vaccination obligatory for the tuberculin-negative population between 15 and 50 years of age. With such energetic attack on tuberculosis, it is hoped that this scourge, which is exceeded only by cardiac and vascular diseases and tumors, and even to-day kills 76 persons per 100,000 population, will soon be brought under control.

BCG VACCINATION IN SWEDEN

The pioneer of BCG vaccination in Sweden is the distinguished pediatrician, Wallgren (12), formerly chief of the Gothenburg Childrens' Hospital and now

chief of the Norrtull Childrens' Hospital in Stockholm. In 1927, Wallgren began a long-term hospital investigation of BCG vaccination of infants born of tuberculous parents. He discarded the oral administration of the vaccine advocated by Calmette, as well as the subcutaneous method practised by Weill-Hallé (13), and administered the vaccine intracutaneously for the purpose of reducing to a minimum the incidence of abscesses at the site of vaccination. With the parents' consent, the newborn infant was separated from its mother immediately after birth and nursed in tuberculosis-free surroundings. If the Mantoux test with 1 mg. OT was negative six weeks after birth, the infant was injected intracutaneously with 0.05 to 0.1 mg. BCG. The strict isolation was continued until tuberculin sensitiveness set in, usually within six weeks after vaccination. At that time the child was restored to its mother with instructions about personal hygiene and for the return of the child to the dispensary for annual tuberculin tests, X-ray and physical examinations.

During the first seven years, Wallgren performed BCG vaccination in close coöperation with the dispensary. Since 1934 the work has been done by the dispensary alone on the same principles as before. Up to the end of 1937 the number of BCG vaccinated children was 1,069 and this material was followed up by Anderson and Belfrage (14) during the winter and spring of 1939. The purpose of this follow-up examination was to ascertain, first, the previous and present state of health of the vaccinated children, especially with respect to tuberculous infection, and, second, their sensitiveness to tuberculin. They found that 15 of the vaccinated children had died of nontuberculous diseases. Biopsy was performed in 9 cases without any signs of tuberculosis, 2 had died from accidents and the remaining 4 of causes which definitely excluded tuberculosis. Only 2 cases of benign tuberculous infection were found among the 1,069 BCG vaccinated children, both of which had healed completely (an erythema nodosum four years after vaccination and a tuberculous pleurisy one year after vaccination). Briefly stated, all vaccinated persons were found to be in good health, X-ray examinations revealed in many cases the presence of minute, very dense, occasionally calcareous spots in the hilum, but no signs of progressive or healed tuberculous processes in either the hilum or the parenchyma were found in a single case, nor in either of the 2 cases just mentioned. Thus 100 per cent of these cases examined were found to be in good health and without any signs of progressive tuberculous disease.

The result of the tuberculin tests was that 97.1 per cent were positive with Hamburger and Mantoux tests and 2.9 per cent were negative. Definite exposure to open tuberculosis had taken place in 397 children, 207 had probably been exposed and 301 had not been exposed and the tuberculin sensitiveness must therefore be ascribed to the BCG vaccination. While the percentage of positive tuberculin reactors among the unexposed children in Gothenburg was only 3.9 per cent, it is obvious that the unexposed BCG vaccinated children show a much higher prevalence of tuberculin reactors than the average figure for Gothenburg. This tuberculin sensitiveness must undoubtedly be regarded as an expression of a relative tuberculosis immunity which in some cases has lasted for more than ten years.

To those who object that no adequate controls were used, Wallgren answers that parents very seldom refuse to consent to BCG vaccination. Among the relatively few cases where BCG vaccination was actually refused, the hospital had 5 deaths from tuberculosis (one tuberculous meningitis and 4 miliary tuberculosis). Thus, 5 deaths from tuberculosis and a few cases of tuberculous disease, the exact number not known, in a material consisting at most of some 10 cases, is admittedly more than occurred in the 1,069 BCG vaccinated children, among whom not a single case of really serious tuberculous disease had occurred. Anderson and Belfrage conclude from their investigation that "it has furnished still further support to the view we have held for some years that in the BCG vaccination we possess a powerful preventive aid against tuberculosis. It is also our intention to strive for a more extensive application of the BCG vaccination, especially among young adults in danger of tuberculous infection."

Such extensive BCG vaccination has been carried out by Anderson and Belfrage among school-children and adults in Gothenburg. At the expiration of 1945 they had vaccinated 41,238 persons, or 10.6 per cent of the city population. No deaths from tuberculosis had occurred among these, while the tuberculosis mortality rate in 1945 was 68 per 100,000 in the city. Twenty-three cases of benign and healed tuberculous disease (7 primary tuberculosis, 11 pleurisies, 2 hilar node involvements and 3 pulmonary tuberculosis) and only one case of progressive pulmonary tuberculosis occurred among the vaccinated group.

Naeslund (15) has vaccinated with BCG 7,765 children in Norrbotten in Northern Sweden. He finds that the tuberculosis mortality rate is less than one-fifth of that among the corresponding group of nonvaccinated children in the same community.

Malmros (16) holds the record of having vaccinated with BCG 40.3 per cent of Ørebro's 42,000 population, namely 15,543 children and adults. Up to March, 1946 no deaths from tuberculosis had occurred and no case of progressive pulmonary tuberculosis was reported among the vaccinated group. He has likewise vaccinated 84 nurses between 1933 and 1945 and has found only one case of healed pleurisy among these.

Tørnell (17), in Boraas, holds the second highest record in Sweden, having vaccinated with BCG 10,279 children and adults between 1934 and 1945, or 25 per cent of the city's 42,000 population. Up to March, 1946 no deaths from tuberculosis had occurred among the vaccinated persons and only 3 cases of benign and subsequently healed tuberculous disease (one erythema nodosum, one pleurisy and one pulmonary tuberculosis).

BCG vaccination has been carried on on an ever-increasing scale in Sweden in recent years. It rose to 84,000 in 1944 and to more than 100,000 in 1945. All conscripts are offered BCG, and nurses are rarely admitted if they are tuberculin-negative and refuse BCG vaccination. The Swedish National Tuberculosis Association is keenly interested in making tuberculin tests and miniature X-ray examination obligatory for the entire population and BCG vaccination for the tuberculin-negative population, irrespective of age. Despite a steady decline in tuberculosis mortality in Sweden from 210 per 100,000 in 1910

to 70 in 1942, the disease plays a most important rôle as an endemic disease. It ranks fourth among the causes of death, being surpassed only by cardiac and vascular diseases, tumors and senile diseases. Tuberculosis exacts an annual toll of more than 4,000 lives, mostly between 15 and 35 years of age. Wallgren (18) is emphatically in favor of universal BCG vaccination in Sweden as a valuable complement to a rational antituberculosis campaign. He is thoroughly convinced that, as long as apparently healthy tuberculosis carriers are ambulatory in the community, so long will BCG vaccination furnish an effective protective barrier against tuberculous disease and this opinion is to-day shared by Sweden's leading tuberculosis experts.

BCG VACCINATION IN DENMARK

Also in Denmark much attention has been paid to the potentialities of BCG vaccination in the campaign against tuberculosis. The pioneers in this field are the distinguished tuberculosis investigator Jensen and his coworkers Ørskov (19) and Holm (20) who have done conspicuous experimental and clinical studies on BCG at the famous State Serum Institute in Copenhagen. After an initial period of anxiety about the instability in virulence of the BCG strain which was sent to them from Paris, the subsequent cultures furnished them have proved completely innocuous and highly effective as a vaccine against a virulent tuberculous infection.

BCG vaccination in Denmark began in 1927 and was reserved for children and adults living in tuberculous surroundings. But it was not until Denmark was drawn into World War II that BCG vaccination was used extensively as an essential weapon against threatening tuberculosis endemics. The background for a more extended use of BCG vaccination in Denmark is essentially the same as in Norway and Sweden, namely that a very large proportion of Danish youth is tuberculin-negative. With exception of South Jutland, bovine tuberculosis is almost completely eradicated in Denmark and on the island of Bornholm. Heimbeck's observation on nurses in Oslo has been adequately confirmed in Denmark where mainly tuberculin-negative persons acquire tuberculous disease when exposed to infection. BCG vaccination has therefore been used on a broad basis in Denmark in order to render these negative tuberculin reactors artificially resistant against an infection with virulent tubercle bacilli.

Reliable data on the tuberculin sensitiveness in various age groups have been collected among pupils in all Danish State Schools and among the conscripts in the army. The average percentage of reactors at 10 years of age is 15.7, at 15 it is 38.1, at 20 it has risen to 58.3 and at 23 years of age 69.4 per cent are tuberculin-positive. In other words, about two-thirds of Danish youths 14 years old are tuberculin-negative and at the age of 20 to 23 years, one-third of the Danish population is still tuberculin-negative.

Holm's (21) study of 1,278 adults and 1,020 children, who were tuberculin-negative and who turned positive and were followed-up by the Central Tuberculosis Dispensary in Copenhagen between 1935 and 1939, shows a great pro-

portion of these "inverters" on the very first examination were found to have demonstrable X-ray changes in the lungs, with tubercle bacilli in the sputum, or more often in the gastric lavage. On further follow-up, a considerable proportion of these persons developed clinical tuberculosis, with progressive lesions in the lungs or in extrapulmonary localizations. Within this four-year period of observations, 9 patients died from tuberculosis, namely one child and 8 adults. She also found that pulmonary tuberculosis usually developed only in persons showing X-ray changes in the lungs shortly after "inversion" had taken place from a negative to a positive tuberculin reaction. About 30 per cent of such adults developed clinical tuberculosis, while only 6 per cent of children "inverters" between 7 and 14 years, and 3 per cent between one and 6 years developed tuberculosis. The disease became progressive always within two years after infection.

The intracutaneous method of vaccination with 0.05 to 0.1 mg. BCG has been used almost exclusively in Denmark. The average prevalence of tuberculin reactors is about 95 per cent two months after vaccination and its average duration is calculated to be four to five years. At that time the vaccinated persons are asked to return for control tuberculin tests and X-ray examination.

On the basis of BCG vaccination of subjects living in tuberculous surroundings, dispensary physicians agree that BCG offers an essential protection not only against the morbid changes following closely upon the primary tuberculous infection, but that it also protects against the more important risk of pulmonary tuberculosis. The experience with vaccinated children intimately exposed to open tuberculous infection shows that tuberculous disease has been reduced to almost nothing after systematic BCG vaccination has been carried through. The previous tuberculosis mortality among children living in this milieu was high. In recent years no children so exposed have died of tuberculosis, and those children who have become ill have had a much milder form of the disease than that previously recorded. This is plainly seen in those vaccinated children who acquire pulmonary tuberculosis. These lesions usually subside within a short time.

The experience of Olsen with BCG vaccination on the island of Bornholm, with a population of nearly 50,000, presents a most important document of the protective value of BCG vaccination against tuberculous disease. As mentioned before, bovine tuberculosis is eradicated on Bornholm and negative tuberculin reactors are more frequent here than anywhere else in Denmark. It was a common experience that, among tuberculin-negative young people who left the island to seek employment or to study in other parts of Denmark, when they returned home later, many of them had contracted tuberculous disease. Since 1937, BCG vaccination has been recommended to all negative tuberculin reactors leaving the island. Since 1940 all the tuberculin-negative young persons residing on the island have been BCG vaccinated, a total of 12,731 persons, or 27 per cent of the island population. The distribution of new cases of tuberculosis on Bornholm during 1936 to 1940, before BCG vaccination was generally enforced, follows the curves seen elsewhere in Denmark. The 134

new cases recorded during this period fell mostly within the age group of 15 to 35. During 1941 to 1945, after BCG vaccination was enforced, the 82 new cases of tuberculosis were evenly distributed throughout all age groups, with a most conspicuous reduction in the age group of 15 to 35. The Danish health authorities ascribe this significant decrease in this important age group to the extensive BCG vaccination.

A study of BCG vaccination of tuberculin-negative medical students at the University of Copenhagen, during the particularly exposed period of hospital service, reveals no pulmonary X-ray changes and no tubercle bacilli in cultures of 175 medical students who were vaccinated with BCG, whereas among 863 tuberculin-negative medical students who were not vaccinated during the same service, 6 per cent showed pulmonary X-ray changes and 2.6 per cent had tubercle bacilli in the sputum or gastric lavage. Among 2,071 tuberculin-positive medical students 0.8 per cent showed X-ray changes and 0.2 per cent had positive cultures of tubercle bacilli.

Holm (20) reports an epidemic of tuberculosis in one of the Danish State Schools in 1942 which furnishes excellent evidence of the protective rôle played by BCG vaccination. This school had 368 girl pupils between 12 and 19 years of age. They had been repeatedly examined for tuberculosis and 133 pupils had been vaccinated with BCG. There were 105 tuberculin-negative pupils who had entered since the last examination and these were not vaccinated with BCG. In January and February, 1943, an influenza-like epidemic broke out almost exclusively among the pupils. As several pupils presented erythema nodosum, the suspicion arose that it might be an epidemic of tuberculosis and a thorough examination was made of the pupils and the school personnel. The source of infection was a female teacher with apical lesions and positive gastric lavage. She was teaching natural science exclusively in a basement classroom with poor ventilation. She did not teach all the classes. The classes which she taught included many whose negative tuberculin reaction had turned positive, as well as cases of tuberculosis. This was likewise true of the classes that occupied the classroom immediately after her lessons. In the classes that were not taught by her and did not come into this room, there were no negative tuberculin reactors who had turned positive, as well as no case of tuberculosis. Follow-up examinations revealed that 40 per cent had X-ray changes and in 35 per cent tubercle bacilli were found as well; clinical pulmonary tuberculosis was found in 6.7 per cent of the 105 tuberculin-negative nonvaccinated pupils. Among the 133 BCG vaccinated pupils, clinical pulmonary tuberculosis was found in 1.5 per cent, and among the 130 naturally tuberculin-positive pupils, clinical pulmonary tuberculosis was found in 3.1 per cent. It is most important to note, however, that the primary phenomena of illness occurred exclusively in the previously tuberculin-negative pupils and in no instance among the BCG vaccinated pupils. This furnishes strong proof for the protective rôle played by BCG vaccination in preventing the morbid sequelae ensuing upon a primary tuberculous infection. In comparing the BCG vaccinated group with the tuberculin-negative group, it is found that BCG vaccination has offered a considerable degree of protection against the development of pulmonary

tuberculosis. By further comparison between the BCG vaccinated group and the tuberculin reactors by natural infection, it appears that BCG vaccination has given at least as effective protection against pulmonary tuberculosis as has a natural infection.

In his concise and fully documented analysis of BCG vaccination in Denmark, which should be read carefully by those seeking first-hand information about this method of preventing tuberculosis, Holm, who is chief of the Tuberculosis Division at the State Serum Institute in Copenhagen, states: "All told, it seems safe to state that BCG vaccination gives an almost complete protection against the morbid conditions accompanying the tuberculous primary infection and also a considerable degree of protection against genuine pulmonary tuberculosis. This protection, however, is not absolute, since in every fairly large group, there will be a few instances of pulmonary tuberculosis among the BCG vaccinated subjects."

A report of February, 1945 (22) shows that BCG vaccination in Denmark during 1940 to 1944 had increased to such an extent that all school-children between 10 and 14 years of age will have been vaccinated with BCG during 1946 and 1947, provided they are negative tuberculin reactors.

Gravesen (23) reports that on February 9, 1946 the Danish Ministry of Health convened a conference of representatives of tuberculosis specialists, pediatricians, school physicians, the State Serum Institute and the general practitioners for a discussion of mass BCG vaccination, as a defense hygienic measure against threats of epidemics from Northern Germany. The conference agreed on launching a campaign for mass BCG vaccination of all tuberculin-negative subjects between 7 and 25 years of age, with follow-up examinations every fourth year and revaccination of all who had turned tuberculin-negative. The pediatricians favored to lower the age limit to 2 years of age. A standing committee was appointed to further this program. It is noteworthy that one of its six members is a general practitioner. The Danish National Tuberculosis Association has in the meantime launched upon a truly gigantic program of BCG vaccination of the entire tuberculin-negative population in Copenhagen, and the same preventive measure is taken by other large Danish cities.

UNIVERSAL INTEREST IN BCG VACCINATION

A noticable change in favor of BCG vaccination is taking place in most other countries of the world, especially in Soviet Russia, South America, Mexico and Canada. The British Medical Journal (24) announces that the British Joint Tuberculosis Council and the Council of the National Association for the Prevention of Tuberculosis have obtained a promise from the British Ministry of Health "to explore the whole question to see if a suitable BCG vaccine could be made available in Great Britain" inasmuch as "there exists in the Tuberculosis Services of Great Britain, and among the medical profession generally, an active and widespread desire that a reliable supply of BCG-vaccine should be made available here, as it has been for years in most other countries of the world." The same editorial laments "that it is much to our discredit that England has contributed nothing to the study of BCG in the human field."

Several sporadic attempts to use BCG vaccination have been made in this country, notably by the late William H. Park and Kereszturi (25) in New York, by Levine and Sackett (26) also in New York, and by Overton (27) in Nashville, Tennessee. But two recent long-term investigations deserve special mention, namely the study by Rosenthal and coworkers (28) in Chicago, and by Aronson and Palmer (29) among North American Indians.

The Chicago project covers a ten-year period of multiple puncture BCG vaccination of newborn infants at the Cook County Hospital, Chicago. Every alternate child was vaccinated with the parents' consent, the time of vaccination being the third to seventh day of life. The follow-up examination at semi-annual intervals consisted of physical examination, tuberculin test and chest roentgenogram. Among 1,204 vaccinated children with no history of definite tuberculous exposure, there were 3 cases of tuberculosis and one death from the disease, whereas among 1,213 controls they found 23 cases of tuberculosis and 4 deaths from the disease. Among 98 vaccinated children definitely exposed to open tuberculosis they found one case of tuberculosis and no deaths, whereas among 63 similarly exposed controls they found 4 cases of tuberculosis and 3 deaths from the disease. Rosenthal and his coworkers conclude from this material that "during the first seven years of life BCG vaccination is of definite value in the prevention of tuberculosis."

Aronson and Palmer's six year's experience with BCG vaccination for the control of tuberculosis among North American Indians comprises 3,007 persons from one to 20 years of age. A group of 1,550 negative tuberculin reactors was vaccinated intracutaneously with 0.05 to 0.1 mg. BCG, and another group of 1,457 tuberculin-negative persons served as controls. No change in the living conditions of the persons in this study, including exposure to tuberculosis, was made either at the beginning or during the study. Both groups were followed-up for six years with annual tuberculin tests and chest X-ray examinations. At the end of this period they found among the 1,550 BCG vaccinated persons 40 cases of tuberculosis and 4 deaths from the disease, whereas among the 1,457 nonvaccinated controls they found 185 cases of tuberculosis and 28 deaths from the disease. In terms of cases of all types and deaths per 1,000 person-years, the rate was 24.3 for the nonvaccinated controls and 4.7 for the group vaccinated with BCG. From this carefully analyzed and meticulously controlled material Aronson and Palmer conclude that "BCG vaccination is associated with marked protection against the development of tuberculosis as measured by mortality and morbidity experiences of the two groups." They also make the significant statement about the duration of immunity conferred by BCG: "There is no evidence from the analysis that a diminution of immunity occurred with the passage of time after vaccination. On the contrary, indications were that the protection may be greater in the later than in the earlier years after vaccination."

On the basis of the pooled international experience with BCG vaccine and the considerable degree of immunizing efficiency of the vaccine as indicated by the most reliable results from other countries, as well as in this country, the United States Public Health Service, Tuberculosis Control Division, is at

present making a serious study of the possibility of using BCG vaccination more extensively in its services.

To those who oppose BCG vaccination because such deliberate imposition of infection implies a certain risk and who insist that only infected persons get tuberculosis, it should be stated emphatically that *BCG vaccination does not imply any risk whatsoever of a subsequent infection caused by the vaccine and yet it accomplishes almost the same protective function against tuberculous disease as does a natural infection with virulent tubercle bacilli.* As an adjunct to the time-honored established antituberculosis measures and without displacing any of these, BCG vaccination commends itself as an effective weapon against tuberculosis among the especially susceptible tuberculin-negative contacts of a tuberculous population.

SUMMARY

BCG vaccination is to-day generally accepted by the medical profession and laymen in Scandinavia as an important adjuvant to established antituberculosis measures because the vaccine is absolutely harmless and produces a relatively high degree of protection against an exogenous tuberculous infection.

Intracutaneous or transcutaneous BCG vaccination renders non-tuberculin reactors tuberculin-positive in more than 90 per cent within two months after vaccination. In the absence of known tuberculous infection, the duration of allergy following BCG vaccination lasts more than five years, although in some instances it may terminate after one year.

During the period of BCG vaccination allergy and exposure to known tuberculous infection, BCG affords an almost complete protection against the morbid postprimary tuberculous lesions and a relatively high protection against secondary tuberculosis including clinical pulmonary disease.

The basis for the concerted Scandinavian mass BCG vaccination is the importance tuberculosis plays even to-day as an endemic disease—the commonest chronic disease in people between 15 and 30 years. Approximately 50 per cent of this age group do not react to tuberculin. These non-reactors have proved more susceptible to progressive tuberculous disease when infected than those in whom a positive tuberculin reaction indicates a previous infection.

BCG vaccination has in recent years been extended from persons intimately exposed to tuberculous infection, such as nurses, medical students, hospital personnel and children born of tuberculous parents, to army conscripts, students between 14 and 30 years and tuberculin-negative reactors in crowded industries and institutions.

Since 1940, more than 100,000 persons have been vaccinated with BCG in Norway, 58,000 army conscripts, and 250,000 civilians in Sweden and 150,000 persons in Denmark.

SUMARIO

La vacunación con BCG se halla hoy día aceptada en general por la profesión y los profanos en Escandinavia como importante coadyuvante de las obras anti-

tuberculosas establecidas por ser absolutamente inocua y evocar una protección relativamente elevada contra una infección tuberculosa exógena.

La vacunación intra o transcutánea con BCG convierte a más de 90% de los negativos a la tuberculina en positivos en término de dos meses. En ausencia de infección tuberculosa conocida la duración de la alergia consecutiva a la vacunación dura más de cinco años, aunque en algunos casos puede terminar en un plazo de un año.

Durante el período de alergia provocado por la vacunación con BCG y de exposición a una infección tuberculosa conocida, BCG ofrece protección casi absoluta contra las lesiones tuberculosas morbosas postprimarias y relativamente alta contra la tuberculosis secundaria, incluso la pulmonar verdadera.

La vacunación concertada en masa con BCG en los países escandinavos básase en la importancia que posee aún hoy día la tuberculosis como afección endémica: la enfermedad crónica más común en las personas de 15 a 30 años de edad. Aproximadamente 50% de ese grupo no reaccionan a la tuberculina, y esos negativos, una vez que se infectan, han resultado más susceptibles a la enfermedad tuberculosa evolutiva que aquellos en los que una reacción positiva indica infección previa.

La vacunación con BCG ha sido extendida en los últimos años, de las personas íntimamente expuestas a la infección tuberculosa, tales como enfermeras, estudiantes de medicina, personal de hospitales e hijos de tuberculosos, a los reclutas militares, estudiantes de 14 a 30 años de edad, y a los negativos a la tuberculina en las industrias e instituciones hacinadas.

Desde 1940 han vacunado con BCG en Noruega a más de 100,000 personas, en Suecia a 58,000 reclutas y 250,000 paisanos y en Dinamarca a 150,000 personas.

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THE CONTROL OF TUBERCULOSIS IN BRAZIL

New Orientation—A New Mentality

MARCIO M. BUENO[1, 2]

Brazil has followed a course of its own in the control of tuberculosis which is worthy of the attention of all those studying this disease. Because the charts showing a high rate of mortality and great number of patients revealed that the epidemic stage had been reached, Brazil planned a campaign to eliminate tuberculosis which differed from those of other countries which had overcome the epidemic stage and had reached the endemic stage.

Particular mention should be made of Brazil's contribution to the world in controlling tuberculosis. In Brazil, for the first time, photofluoroscopy was done in an effective manner and this important discovery was used in making mass examinations of the chest. Vaccination with BCG is being used extensively and methodically in Brazil.

The basic elements for a modern way to control tuberculosis in Brazil were born or led to a certain and definite result. Brazil is also very active in the treatment of tuberculosis.

Brazil has few beds in tuberculosis institutions compared with the tuberculosis mortality, but the quality of hospitals is of a high order. There is Belem Sanatorium in Rio Grande do Sul, Santa Maria Sanatorium in Rio de Janeiro, Santa Therezinha in Bahia, Benjamin Guimarães Foundation Sanatorium for children in Belo Horizonte, Belo Horizonte Sanatorium in the same city, Correas Sanatorium in Petropolis, etc.

Economic protection for the tuberculous patient and his family is not overlooked. Every sick public employee or employee associated with a beneficiary institution of the Ministry of Labor (commercial, industrial, maritime, financial, etc.) may have initially two years of observation and treatment for which he does not pay (free treatment and, if necessary, care in a sanatorium). In case he is not cured, he is retired with full monthly pay, or with a pension which is in proportion to his time of service. In case the relatives of the employee contract the disease, they also have free treatment.

HISTORICAL BACKGROUND

The Brazilian League against Tuberculosis, founded in 1900, to-day functions under the name of *Fundação Ataulfo de Paiva* and was the first National Tuberculosis Association on the American Continent.

In 1908 Cardoso Fontes reported his discovery of the tuberculous "ultravirus," the concept of which was adopted by the French School (Vaudremer, Valtis and Calmette) in 1921; however, it was not accepted by the majority of

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the tuberculosis specialists. Fontes was credited with clarifying many obscure points in the developmental cycle of the Koch bacillus.

In 1912 Clemente Ferreira established a dispensary in São Paulo, which to-day bears his name. It is modeled after the one in Edinburg designed by Sir Robert Phillip. Artificial penumothorax was brought to Brazil by Oliveira Botelho. However, in view of the poor results obtained, it was abandoned. It was Edgar Abrantes of Rio de Janeiro who introduced it scientifically and he was soon followed by Mazzini Bueno (1914) and others.

The first government department to take a real interest in the control of tuberculosis was the *Inspectoria de Prophylaxia da Tuberculose* of the National Department of Public Health, in 1922, directed by Placido Barbosa. Until then, tuberculosis was diagnosed only in its late stages and usually by clinical methods. Only very few physicians used X-ray diagnosis. At that time the treatment consisted principally in bed-rest. There was not even one sanatorium for indigent people who were very sick. However, the hospitals of São Sebastião and Paula Candido, in Rio de Janeiro and Niteroi, respectively, had some wards for isolation purposes. Mazzini Bueno was in charge of the first building for tuberculous patients at the São Sebastião Hospital. Generally the rich went to Switzerland for treatment.

Placido Barbosa began intensive propaganda on sanitation and stressed the need for treatment in the dispensaries. He invited Mazzini Bueno to apply and teach pneumothorax. In the only dispensary of the *Inspectoria*, the first Brazilian School of Tuberculosis was founded, in which, as in all other schools established in Brazil to date, clinical care was stressed more than prophylaxis. Together with Mazzini Bueno, Genesio Pitanga (who later succeeded Placido Barbosa as director of the *Inspectoria*), Ary Miranda, Alexander Stokler and Feliciano Motta worked in the *Inspectoria;* all of them are to-day specialists of great renown.

At the suggestion of Mazzini Bueno, Placido Barbosa invited Manuel de Abreu, a Brazilian physician, already recognized in France as a radiologist under Professor E. Rist, to take charge of the X-ray section. Abreu later became famous for his invention of photofluorography. Alberto Renzo, then at the Hospital of São Sebastião, came to the *Inspectoria* to observe pneumothorax treatment.

The *Inspectoria*, besides giving clinical care, making X-ray surveys and propaganda on sanitation and statistics, began to utilize visiting nurses who go to the homes of the sick, look into the hygienic conditions, advise the family, suggest examination of contacts, etc. Since that time, notification of tuberculous patients became obligatory. With the increase in service rendered, the *Inspectoria* built another dispensary in Botafogo and later many others. However, no more dispensaries were constructed to take care of tuberculous patients only. Instead there are now "health centres" for each district which serve several purposes, including tuberculosis.

In 1925 the first department of tuberculosis in a medical school of South America was created in the Fluminense Medical School and Mazzini Bueno was

appointed professor. In 1919 Carvalho Leite built the Palmyra Sanatorium. At the beginning of the year 1925, other sanatoria were organized and, also under the influence of the Swiss experience, special climatic conditions were chosen as locations. In Correas, the Sanatorium of Correas was built by Valois Souto. In Belo Horizonte, Samuel Libanio built the Belo Horizonte Sanatorium, Hugo Werneck the Werneck Sanatorium, Alberto Cavalcante the Cavalcante Sanatorium and later the Minas Geraes Sanatorium. In Campos do Jordão and São José dos Campos (State of São Paulo) various sanatoria began to function. However, they were run on a different basis than those just mentioned. They took in non-paying patients as well as paying patients, as they are endowed by private associations. Those previously mentioned treated only paying patients. In Petropolis the Nogueira Sanatorium for tuberculous children began to function and was the first of its kind in South America (Director, Dr. Campbell Penna). In Campos do Jordão, São José dos Campos and Belo Horizonte, there were specialists who to-day are very well known—Souza Lima, Nogueira Cardoso, Paula Souza, Glovis Correa, Queiroz Telles, Pardomeo, Ruy Doria, Nelson Davila, Mario Pires.

In 1927, the first new-born child was vaccinated with BCG by Arlindo de Assis in Rio de Janeiro, in what was then the Brazilian League against Tuberculosis.

Clementino Fraga, who from 1926 to 1930 was director of the National Department of Public Health, reformed the hospitals of São Sebastião and Paula Candido and, in 1929, started a course on tuberculosis for postgraduates of the University of Brazil. Fraga's assistants in the University, eminent European and Latin-American professors and the clinical staff of São Sebastião got together to teach this course which was given for twelve consecutive years. Mazzini Bueno and Alberto Renzo were at the head of the staff. This course was the principal source of specialists in tuberculosis in Brazil. Fraga also formed and organized the Department of Tuberculosis in the City of Rio de Janeiro (1938).

The first thoracoplasties were performed with good results by Rodolpho Josetti in 1925, and in 1930 Pardomeo did the first pneumonolysis in Campos do Jordão. Pinheiro Guimarães, Amorim, Paulino, Marques Lisboa, Gontijo, Vasconcellos, Comenale, Correa Neto, Etzel, Pardal, Azambuja Lacerda, Sisson, C. Branco, are now our best thoracic surgeons—some of them with a long training in the U.S.A.

In 1929, Affonso MacDowell began to supervise the department of tuberculosis in the General Polyclinic of Rio de Janeiro (out-patients, private institution and one for non-paying patients). MacDowell succeeded in organizing a body of assistants who made up one of the most brilliant schools of tuberculosis in Brazil and founded the *Brazilian Review of Tuberculosis*. (Later the *Paulista Review of Phthisiology* was founded in São Paulo.) The service rendered by the Polyclinic for tuberculosis is essentially therapeutic and is extremely good. It also has one of the best surgical departments.

Between 1930 and 1944, the control of tuberculosis was very active. In all the states and in most of the important cities, dispensaries were built and the

number of beds greatly increased. Departments of tuberculosis were created in Rio de Janeiro and São Paulo, the former having as its first director, Helio Fraga and the latter Decio Queiroz Tellos. The number of departments of tuberculosis increased in the medical schools, among them that of A. Ibiapina in the Medical and Surgical School of Rio de Janeiro. The Federal Government created the National Tuberculosis Division whose first director was Samuel Libanio. He tried to standardize the control measures; he built several sanatoria and dispensaries and he made mass X-raying of the chest and vaccination with BCG more extensive. With the forming of the National Labor Department under the Vargas government, all working classes, except farm workers and domestic servants, came to have protection under the social legislation. This guarantees them employment and medical and financial assistance. In 1931 the Brazilian Society of Tuberculosis was founded, to which all the physicians specializing in this field congregated monthly. In 1939, under the presidency of Ary Miranda, the first National Congress on Tuberculosis was held, and in 1941 the second, under the presidency of R. Paula Souza and U. Nonohay. Two additional facts might also be mentioned here. First, Jose Silveira founded an Institution of Tuberculosis in Bahia, more for the purpose of research and teaching, similar to those already existing in Argentina (Prof. Sayago), Uruguay (Profs. J. Morelli and Fernando Gomez) and the Henry Phipps Institute in Philadelphia. Second, "subtilina," an antibiotic extracted from the *Bacillus subtilis* was developed and studied. The use of this preparation has shown promising results in the treatment of tuberculosis in guinea pigs, but Fontes Magarão, who is studying it, cannot yet say anything definite as his studies are still in the experimental stage.

I now wish to call attention to the following facts relating to the control of tuberculosis which created a *new mentality:*

(*1*) In 1935, Manuel de Abreu succeeded in developing a practical and economical method for mass radiography of the chest. Abreu is not only credited with the discovery of roentgen-photography (also called fluorography, photofluoroscopy, microfilm, abreugrafia, Abreu, 35 mm., etc.), but he was also the first person to have the idea of how to use this in chest examinations in a whole community.

The idea of mass X-ray surveys of the chest is quite old. In 1897, Kelsh and Boinon proposed that mass X-raying of the chest be made obligatory. A few years later, an assistant of Beclère made the first radiological chest examinations on more than 100 French soldiers. Until 1935, however, the methods used were not completely satisfactory. Fluoroscopy is inaccurate, its margin of error is large, and the operator can make only a limited number of examinations daily, not only because of the time necessary for each examination, but also because of the dangers of secondary irradiation. The common radiography is expensive and the use of paper film, although cheaper than film, is still quite expensive. This latter method resulted in an appreciable margin of error and, from a practical and economical point of view, it cannot be compared with photofluorography.

Photofluorography was tried almost immediately after the discovery of X-

ray (Bleyer); however, without satisfactory result. Only in 1935 did Abreu succeed. The first mass survey was made by him with the assistance of Paulo Cortes in 1936–1937 at Health Centre No. 2, in Rio de Janeiro. Afterwards, the person who worked most closely with Abreu was Aloysio de Paula. In 1938 Rodolpho Vacarezza and Sayago introduced the method in Argentina, David O. N. Lindberg in the United States, and Holfelder in Germany, after they visited Brazil, watched the apparatus and studied the researches of Abreu. Without any doubt, Abreu initiated this method and, if to-day technical improvements are suggested, the basic principle remains the same.

In Brazil, all those who work with food are required to have an X-ray examination once every six months. In case they do not present to the government authorities their certificates signed by the Health Centre, the company for whom they work is penalized and the employee suspended. All new employees of every government office (federal, state or municipal) or employees affiliated with beneficiary organizations of the Labor Department are required to have a chest examination by photofluorography. The same examination is given to soldiers and students. Now, only domestic servants and those in rural districts can avoid this examination. The survey must be made annually as it is only of value if made at regular intervals. In X-ray surveys, nonapparent forms of tuberculosis are found. The term "nonapparent," introduced by Luiz Sayé, means that tuberculous patients may appear to be healthy since they have no symptoms. Nonapparent tuberculosis is discovered only by X-ray examination. The term "imperceptible tuberculosis," suggested by Braeuning, is based on a psychological concept and signifies tuberculosis, regardless of its state and signs, but which is not perceived by the patient. Nonapparent tuberculosis indicates that pulmonary tuberculosis has a silent stage, which may be very long. Mass X-ray surveys make possible the diagnosis of the initial stages and their early treatment. They also have a highly prophylactic and social function, because they eliminate the greater number of sources of contagion and leave a greater number of useful individuals to society. As we know, in a general way, arrest of tuberculosis is most probable in patients with minimal lesions.

In Brazil, the results show that about 3 to 5 per cent of those examined have active pulmonary tuberculosis. Before mass X-ray films of the chest were used, the number of cases was calculated on the basis of mortality according to North American studies. For one death from tuberculosis they estimated that between 5 to 10 tuberculous patients were alive. A problem which already existed before X-ray surveys were made, but which became greater, was how to isolate those with tuberculosis and how to eliminate the sources of contagion. First, it must be taken into consideration that a large proportion are patients with minimal lesions and can receive treatment in the dispensaries. In 1944, Abreu, in trying to find a solution to the problem of hospitalization, suggested having villages similar to colonies, where tuberculous patients were obliged to go to live. This solution has innumerable advantages over the construction of very expensive sanatoria which are also very expensive to maintain. It also solves the problem

of rehabilitation. Abreu's idea was not original. In 1939, I made the same suggestion to the First Brazilian Congréss of Tuberculosis, held in Rio de Janeiro, and long before this there was a very successful colony in Papworth, England.

Another problem which X-ray surveys brought to light was the great number of cases with "shadows in the lungs" for which the diagnosis was not known. Many persons interrupted their careers and their work, while their physicians tried to arrive at a definite diagnosis, and the general tendency was for them to retire. Abreu suggested pulmonary lavage to search for tubercle bacilli. Saline solution was injected through the cricoid-thyroid membrane. This technique caused some accidents and was abandoned. The supraglottic method is simple and harmless. It was performed for the first time in Brazil by R. Fernandes. In comparison with the method of gastric lavage it reveals a greater number of positive results. However, I believe that this method ought to be practiced with reserve, as it can easily cause tuberculosis to spread into normal parts of the lungs. Fernandes found, in 8 per cent of his patients in whom lung lavages had been done, small foci of pulmonary inflammation which caused pain in the chest for some days following lavage.

What X-ray studies have really demonstrated is that all types of tuberculosis can be detected roentgenologically. From the static phase, waiting for the patient with symptoms of tuberculosis to come to the physician, we passed to the dynamic phase of search for tuberculous patients by compulsory examinations of contacts in dispensaries, and finally to mass radiography of the chest, first of collective groups and later of everyone, which is the actual modern stage, brought about by the investigations of Abreu.

(*2*) Brazil, a country larger in area than the U. S. A., has over 45,000,000 inhabitants. Most of its population is near the coast with the densest districts in the southeast. The tuberculosis mortality is 250 for 100,000. In other words, about 112,500 die yearly from tuberculosis. At an optimistic estimate of 5 patients for each death, we expect 572,000 patients yearly. Tuberculosis is the first cause of death according to these statistics.

The standards of the sanatoria and hospitals are in general good and comparable to those of other countries with good control measures. The number of beds, however, is very small. Even in the capital, Rio de Janeiro, where we have the largest number of beds, we still do not have one bed for each death from tuberculosis. The State of São Paulo, noted for its efficient hospitalization, has not yet reached the necessary number of beds. If in a rich country, such as the U. S. A., Herman Hilleboe, the Medical Director, Chief of the Tuberculosis Control Division, speaks about the "tremendous investment of hospitalization," it will not be hard to understand that in Brazil it would be almost impossible to build and to maintain enough hospitals and sanatoria to hold an adequate number of beds.

The fight against tuberculosis in a country in which tuberculosis is in the epidemic phase is completely different from that in a country in which it is in the endemic phase with a minimal death rate for tuberculosis (residual or basal rate according to Hoffbauer). In the latter type of country periodic mass X-

ray surveys of the chest will certainly complete the tuberculosis control and will reduce the mortality to an insignificant number. Such countries need not fear immigrants and visitors who may import the disease, if they are submitted to obligatory medical examination. I think they will have only two problems: (*1*) the nonallergic persons who are going to live in foreign countries where tuberculosis is in the epidemic phase, and (*2*) nonallergic persons who work in hospitals and sanatoria, especially young medical students, physicians and nurses.

Our great need is to protect the healthy people. Because we do not have sufficient beds to isolate the sick, we try to use some more economical measure, which *for us* is more practical.

We believe that one of the methods which gives good protection to healthy persons against tuberculosis is to make him allergic. Morbidity and mortality for tuberculosis are much lower among allergic than among nonallergic persons. A series of statistics, among which are those of Heimbeck, Scheel, Rist and Tuchila, Saye, confirms this opinion. On the other hand, the statistics of Myers, Harrington and the South African Commission, which concluded with the contrary opinion, cannot be accepted, as Sayago has demonstrated (see volume de Tisiologia, 1940, Buenos Aires).

Sayago (1939, Tisiologia, Buenos Aires), in an anatomical and epidemiological study, reached the conclusion that the fight against tuberculosis in South America is a fight against primary infection (primary *progressive* tuberculosis). The mortality statistics for tuberculosis in Brazil reveal that the highest mortality rate occurs during the first years of life, that then a drop occurs and a later rise during adolescence, followed by another drop after the twenty-fifth year. The age groups in which the mortality is highest are just the ones in which there is the greatest opportunity for contact of nonallergic persons with sources of infection. These are the children, in the first place, and, second, young adults who move to large cities for study or work. The epidemiological investigations in Brazil reveal a high rate of nonallergic persons in rural and semirural areas and an average rate in large centres of population. Also the number of adults who die as a result of primary progressive infections is large.

A German pathologist, Bungeler, who performed autopsies on adults in the hospital of São Luiz de Gonzaga in São Paulo, found typical forms of primary progressive tuberculosis, some of which developed from a secondary complex. He thought that he had found a "tropical type" of tuberculosis. This so-called "tropical type" was considered to be a serious primary progressive tuberculosis, Borrel type. His studies were later confirmed by R. Fernandes, Poppe de Figueiredo and associates. In 314 autopsies of adults, Fernandes found 67.1 per cent cases of primary progressive complex and 32.9 per cent cases of re-infection type.

Among Fernandes' cases, 271 were women and 43 men; 113 were white, 84 Negroes and 117 Mulattos; 9 were foreigners and 305 Brazilians. Of the Brazilians, 76 were born and always lived in a large city, Rio de Janeiro, and 229 lived first in rural and semirural zones and then went to live in Rio de Janeiro,

where they remained from six months to ten years. Particularly in those who had lived in rural and semirural areas was primary progressive tuberculosis found.

Tuberculosis is a disease of civilization. Isolated people who have not had contact with tuberculosis are rapidly attacked. In this early phase of tuberculization, morbidity, mortality and infection rates are low. In the next phase of massive tuberculization there is a high mortality, a high rate of morbidity and a high rate of infection. Third, comes the phase of decreasing tuberculization with deaths and illness declining, but infection remaining high for a long time. It was Louis Sayé who thus defined the different epidemiological phases of tuberculosis. The average mortality rate for tuberculosis in Brazil is about 250 for 100,000, but in some cities of the coast the figures are higher than that: Recife, the capital of Pernambuco State, and Victoria, the capital of Espirito Santo State, have over 400 for 100,000. On the other hand, some cities of the middle-western states have lower figures. Cuyabá, the capital of Matto Grosso State, and Therezina, the capital of Piauhy State, have 70 for 100,000. Recife is in the phase of massive tuberculization. Victoria has a high mortality, but the index of infection, about 60 per cent of the population, indicates that many of the deaths from tuberculosis are in people of another city or town. It has not yet reached the phase of massive tuberculization. Cuyabá and Therezina have very low infection rates; but if some efficient measure is not taken rapidly, they will enter in the phase of massive tuberculization. The end of the wave of tuberculization leaves the people with a high rate of infection, low morbidity and low mortality, which means that these infected people have more resistance against tuberculosis than those who are not infected when they are initially hit by the disease. *Therefore why not confer that resistance by infecting the people without danger to them?* We, in Brazil, feel that this can be done by giving the people mild primary infections with bacilli of attenuated virulence that do not produce progressive disease.

The best means of allergizing a person is through the administration of BCG. In Latin America, especially in Brazil, the majority of our specialists favor vaccination with BCG. In support of this assertion I shall translate the first conclusion of the first "theme" of the Sixth Congress of the Latin-American Union of the Societies of Tuberculosis, composed of delegates from twenty Latin-American countries, which was held in Havana, Cuba, from the 15th to the 21st of January, 1945.

First theme: *Position of BCG Vaccine in the Prophylaxis of Tuberculosis.*

The final conclusion which the delegates, Dr. Vargas Sivila from Bolivia, Dr. Sanchez de Fuentes from Cuba, Dr. A. Ginez from Paraguay, Dr. Garcia Rossell from Peru and Dr. Abelardo Saenz from Uruguay, submitted for approval to the Executive Committee of the Congress read as follows: "It has been demonstrated universally that it is possible to obtain immunization against tuberculosis, both in experimental medicine and in the human clinic, and it has also been proved that BCG vaccination is harmless and beneficial; therefore the ULAST recommends wider use of the vaccine in healthy nonallergic people from the first day of life, by mouth or by inoculation. In order to obtain the most favorable results, the

vaccination should be made under the best conditions—absence of tuberculous infection in the person vaccinated and prevention, as much as possible, of virulent infections in the period following the vaccination." (It should be mentioned that there are over 600,000 people who have been vaccinated in the Latin-American countries.)

These conclusions were unanimously approved by more than 300 delegates, representing all of the twenty Latin-American countries, among whom were G. Sayago (Argentina), Fernando Gomes (Uruguay), Orrego Puelma (Chile), Juan J. Castillo (Cuba), Cossio Villegas (Mexico) and Garcia Rossell (Peru).

BCG was first used in Brazil in 1927 and we already have more than 340,000 persons vaccinated, 164,152 in Rio de Janeiro alone. Arlindo de Assis presented statistics concerning the latter group on January 10, 1945 at the Sixth Pan-American Congress of Tuberculosis in Havana, Cuba. That BCG is harmless is no longer disputed. Human experience is the most valuable proof. Of all those vaccinated in Brazil, there is not even one who has become ill as a consequence of BCG.

All twenty states and the Federal District in Brazil have clinics for vaccination with BCG. Seven states have organized laboratories for making the vaccine, the Federal District, Rio Grande do Sul (two laboratories), São Paulo, Bahia, Rio de Janeiro, Pernambuco and Rio Grande do Norte. The other fourteen are supplied with vaccine which the Fundação Ataulpho de Pavia (Brazilian Anti-Tuberculosis League) sends weekly by air. The Federal District has the first clinic which is also the largest. One building houses the laboratory for the preparation of the vaccine and all work in connection with BCG, including the control of children vaccinated by pediatricians with a knowledge of childhood tuberculosis. The Foundation has a special course for nurses in the administration of BCG. It is these nurses who vaccinate every new-born child, be it in the hospital or at home. Assis is vaccinating over 50 per cent of the new-born in the Federal District. Since 1932 the Public Health authorities have adopted BCG in their program. At present the National Department of Health in Brazil, Division of Tuberculosis, distributes BCG prepared by Assis to the states. In the Federal District, the Tuberculosis Department of the Local Health Division under the direction of A. Renzo is vaccinating, in coöperation with the Foundation, all the nonallergic persons regardless of age. Every Health Centre has the vaccine. In almost every state the local Public Health Centres are coöperating. Students, workers, sailors and soldiers have been vaccinated. Their number has already reached several thousand.

Assis and the Brazilian physicians prefer oral vaccination. Assis recommends as *essential conditions* the following: (*1*) use of recently prepared vaccine, grown for twelve to fourteen days at 37° C.; (*2*) the use of large doses of bacilli (from 90 to 200 mg. wet weight); (*3*) the use of Sauton diluted 1:4 with a pH carefully adjusted to 7.1 or 7.3 (average 7.2); (*4*) proper administration of the vaccine to persons who have not eaten since the previous day before breakfast. They may eat after one-half or one hour following vaccination.

Attention is called to the fact that the dose recommended by Calmette was

30 mg.; the recommended period of growth was twenty-five days. The modifications Assis made with vaccination by mouth achieved the same efficiency as subcutaneous or intracutaneous vaccination. Following are Assis' conclusions regarding the ways of administration: (*1*) Subcutaneously, in doses of 0.01 to 0.1 mg., in nonallergic children, BCG caused only local reactions, moderate and transitory, with 4 per cent of the reactions more severe. In 92 per cent of the cases tuberculin allergy of a slight degree developed; it was rarely moderate; and 8 per cent of those vaccinated remained apparently nonallergic. Never were general reactions observed. (*2*) After a dose of 0.1 mg. given intracutaneously to nonallergic children, BCG provoked a small local reaction, which in some cases was followed by a transitory abscess without general reactions. The Mantoux test with 5 mg. of tuberculin, within the first sixty days after inoculation, was positive in 77.78 per cent and negative in 22.22 per cent. (*3*) Given *by mouth* in three doses of 20 to 30 mg. each, to the new-born (first ten days), BCG did not cause any disturbance and produced tuberculin allergy which started in the third week after vaccination in 15 per cent of the cases. The number of allergic children increased, reaching 83.94 per cent in the fourth month of life, and 87.72 per cent in the sixth month of life. These data were taken from material gathered over a period of twelve years (1928 to 1939) on 4,389 vaccinated children who had no contact with tuberculous patients.

With one dose of 200 mg. by mouth before breakfast, administered to persons of various ages, excluding those of six months and under, Assis obtained 68.52 per cent positive Mantoux tests, 20.53 per cent incomplete or dubious results and 10.95 per cent negative results.

Except in the new-born, we always test for so-called "infratuberculin allergy" before the administration of BCG to persons with negative Mantoux tests, up to 10 mg. of OT. An intracutaneous injection of 0.1 mg. of heat-killed BCG is given. "Infratuberculin allergy" is assumed to be present if a premature and extensive local reaction develops. In such cases tuberculin allergy develops in the first week after that injection. Assis[3] found "infratuberculin allergy" in 76.2 per cent of persons already vaccinated with BCG but with negative Mantoux tests. In those not vaccinated and apparently nonallergic, the incidence of "infratuberculin allergy" is much lower.

Assis uses the strain "Moreau" of the bacillus of Calmette and Guérin, studied in our laboratories more than nineteen years and in the human being more than seventeen years. This strain keeps its attenuated virulence, is tuberculinogenic and produces allergy.

Among the workers who experimented with BCG, some are incredulous and disillusioned as to its beneficial effect. They are those whose first experiences were poorly planned and they failed either because the preparation of the vaccine was not properly done or because they did not know how to administer the vaccine. Whoever inoculates children, who before vaccination and during the

[3]See Assis: O Hospital, Rio de Janeiro, August and December, 1942; October and December, 1943.

preallergic period were in contact with tuberculous people, does not properly vaccinate. It is logical that many of these children were infected with bacilli before BCG could allergize them. Other failures were due to the original recommendation of Calmette. He recommended a total of 30 mg. and cultures which were twenty-five days old. Small oral doses of BCG which have little vitality allergize only a small proportion of the recipients.

To reach definite and unquestionable conclusions regarding vaccination with BCG, and to convince all the specialists of its advantages, is something that will require a long time to accomplish. Anyway, the Brazilian vaccination is extensive, well planned and rigorously carried out and it deserves the consideration of everyone.

In an attempt to protect the healthy people, we think that the fundamental goal for control of tuberculosis is to eliminate the source of contact and it is necessary:

1: To discover it.
2: To make it harmless.
   (a) Directly, either by isolating the patients or by proper medical treatment.
   (b) Indirectly, by giving to the healthy people a means of defense, in order to make them able to meet the contacts without harm.

Of course, medical care and vaccination have double finalities; one is social—the avoidance of the spreading of tuberculosis; the other is medical—to cure the patient with the former and to defend the individual with the latter. Each method complements the other and in Brazil we use those which we consider to have technical, economical and practical advantages *for us*.

We need to do obligatory and periodic (yearly) mass X-ray surveys of the chest, tuberculin tests on the healthy, vaccination of the nonallergic (especially of the new-born) and early treatment of the sick, preferably in out-patient clinics. The dispensary is for us the most important foundation for the control of tuberculosis; dispensary with Abreu apparatus for mass X-ray surveys, with pneumothorax clinic and with a *separate* section for BCG.

SUMMARY

1. Initially, the control of tuberculosis in Brazil meant essentially treating the sick, almost always in far advanced stages. It meant late diagnoses and, therefore, indefinite treatment. This phase of tuberculosis work was the static state.

2. Then there was the search for the sick in persons in contact with patients, dissemination of advice, treatment and isolation of the tuberculous patients. This was the beginning of the dynamic phase.

3. Finally, we sought for nonapparent tuberculosis. Now there is the periodic and obligatory X-ray survey of the chest for everyone, with early diagnosis and early treatment of the tuberculous patients. Also there is vaccination with BCG, especially of the new-born. There is the search for the nonallergic in persons older than twenty days. This work coincides with the economic pro-

tection of the sick and his family. This is the dynamic phase of the tuberculosis control in Brazil.

SUMARIO

1. Al principio, la lucha antituberculosa en el Brasil venía a ser tratamiento de los enfermos, casi siempre en los períodos muy avanzados, y desde luego diagnósticos tardíos, y por lo tanto, tratamiento indefinido. Esta fase de la obra antituberculosa constituyó la etapa estática.

2. Vino después la busca de los enfermos entre los convivientes con los enfermos, la diseminación de consejos, y el aislamiento y tratamiento de los tuberculosos, comenzando así la etapa dinámica.

3. Por fin, comenzó la busca de la tuberculosis inaparente. Ahora tenemos las encuestas roentgenográficas periódicas y obligatorias del tórax, para todos, con el diagnóstico y el tratamiento tempranos de los tuberculosos. También se cuenta con la vacunación con BCG, sobre todo de los recién nacidos. Hay además la pesquisa de los analérgicos en los niños de más de 20 días de edad. Estas medidas coinciden con la protección económica del enfermo y la familia del mismo. Esta es la etapa dinámica de la lucha antituberculosa en el Brasil.

INTRAVENOUS INFECTION OF THE CHICK EMBRYO WITH TUBERCLE BACILLI[1,2]

Inhibitory Effects of Streptomycin

HENRY F. LEE AND ABRAM B. STAVITSKY[3]

A number of studies have been reported concerning the response of the chorio-allantoic membrane of the chick embryo to inoculation with tubercle bacilli of human, bovine, avian and other types. Such inoculation regularly produces tubercle-like infiltrations in the membrane mesenchyme. By this method infection is limited almost entirely to the extra-embryonic membrane (1, 2, 3). Canat and Opie (4) have described the results of direct percutaneous inoculation of the body of the embryo with avian bacilli.

In the course of studying certain compounds for their tuberculostatic properties it became desirable to produce roughly quantitative infection of the *chick embryo itself* with human tubercle bacilli. It was felt that, if such infection could be regularly reproduced within the parenchymatous organs of the embryo, it would lend itself readily to chemotherapeutic experiments of certain types.

In a previous paper (5) a technique for intravenous injection of the chick embryo was described and quantitative data on drug-levels obtainable in the blood and extra-embryonic fluids were presented. The present report includes a brief discussion of the various possible routes of infection of the chick embryo but deals chiefly with the histopathology of infection produced by the intravenous injection of human tubercle bacilli. The effects of streptomycin in inhibiting the development of infection produced by intravenous inoculation are described.

MATERIAL AND METHODS

A human strain (A-27-Phipps) of *Mycobacterium tuberculosis* was used exclusively in the studies here reported. This strain was isolated from a patient in 1938 at the Henry Phipps Institute in Philadelphia. It was then maintained regularly on 3 per cent glycerol agar slants but occasionally was cultivated for several generations on Dorset's medium. Throughout the present experiments it was maintained on a modified Loewenstein's bone marrow infusion medium (11). The strain is of relatively low virulence for guinea pigs: 0.5 mg. injected intraperitoneally into guinea pigs produces generalized and usually fatal tuberculosis in six weeks to two months.

The embryos were infected intravenously by means of suspensions containing known numbers of bacilli per unit volume. Actually it is more accurate to speak of known numbers of bacillary particles since, although the particle size in the suspensions was very small, it is not possible to state that each particle contained only a single bacillus. Fourteen day old cultures were always used. All solutions and equipment used in the preparation of suspensions were sterile.

[1] From the Children's Hospital of Philadelphia (Department of Pediatrics, University of Pennsylvania), Philadelphia, Pennsylvania.

[2] Supported by a grant from the Heyden Chemical Corporation.

[3] Present address: Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena 4, California.

The dry growth of bacilli was weighed out on a sheet of platinum foil. The mass of bacilli was next ground in an agate mortar with a drop of ox-bile which aided in dispersion and uniform suspension. To this mixture sterile physiological saline was added with constant grinding. The resultant suspension was filtered through Whatman No. 5 filter paper which removed all but minute particles.

The filtrate was then adjusted to contain approximately the desired number of organisms by counting the particles in a Petroff-Hauser counting chamber with darkfield illumination and by then diluting the filtrate to the desired particle concentration with physiological saline solution. As a further check on the number of bacillary particles in the suspensions, known volumes of the serially diluted suspensions were planted on modified Loewenstein's bone marrow infusion media slants as described by Lurie (10). Reproducible colony counts were consistently obtained by this method and checked sufficiently well for our purposes with the particle counts made in the chamber.

The technique of injection of the eggs, which has been described elsewhere (5), is briefly as follows: The shell over the entire airsac is removed and the reflected portion of the shell membrane stripped from the underlying chorio-allantois. The embryonic sacs and allantoic veins are then clearly visible and selective or combined intravenous, intra-yolk, intra-amniotic or intra-allantoic injections or aspirations may be accurately made; 0.05 cc. of fluid may be injected into very small allantoic venules. The open end of the egg is sealed with three layers of transparent Scotch tape through which the embryo remains visible permitting ready determination of its death without candling.

In the present studies dealing with the histopathogenesis of tuberculous infection, eggs were used which were of ten days' incubation at the time of inoculation. In the experiments utilizing streptomycin, eggs of twelve days' incubation were used. In all the experiments the surviving eggs were opened on the twentieth day of incubation, the embryos removed and the various tissues saved for culture or histological sections. For histological preparations the tissues were fixed in 10 per cent formalin, imbedded in paraffin and sectioned.

Sections were stained by the Ziehl-Neelsen method and were counterstained with hematoxylin to bring out nuclear detail. Adjacent sections were stained with hematoxylin-eosin to facilitate the study of the nature of the lesions.

INFECTION OF THE CHICK EMBRYO WITH HUMAN A-27 TUBERCLE BACILLI

A. *Infection via the exposed surface of the chorio-allantoic membrane:* In the course of preliminary studies several experiments were carried out which involved the direct implantation of A-27 tubercle bacilli upon the exposed chorio-allantoic membrane of 9-, 10- and 11-day embryos. The results of similar studies have been reported in great detail by Moore (1) Emmart and Smith (2) Fite and others (3). Our findings were in agreement with these previous studies. In several reported chemotherapeutic experiments it has been shown that the number of nodules produced in the membranes by infection with a known dose of tubercle bacilli can be influenced by the coincident use of certain globulins or other compounds including streptomycin (8, 9, 10).

We have paralleled our studies of intravenously produced infection (see below) with studies of membranes infected by direct inoculation with 0.2 cc. of a saline suspension of bacilli containing approximately 10 million bacillary particles (approximately one-sixth of a milligram of a fourteen-day culture). This dose was

established after trying a wide range of dosage and finding that the above produced a fairly uniform infection with well separated discrete nodules. Larger doses, in our hands, produced massive infection of the membrane which was more difficult to evaluate in any quantitative fashion.

The implantation of the surface of the membrane is a somewhat simpler technique than is intravenous injection but the latter makes possible the production of infection within the parenchymatous organs of the embryo. As will be shown later, the various organs respond somewhat differently to the presence of the bacilli.

B. *Infection by injection into the amniotic fluid:* The injection of 0.25 cc. of a suspension of A-27 bacilli (containing 2 mg. of bacilli) into the amniotic fluid does not produce infection of predictable extent in the parenchymatous organs of the embryo. Of 5 embryos surviving to the nineteenth day after an intra-amniotic injection had been made on the ninth day, only one showed very slight evidence of infection in the liver.

C. *Infection by injection into the yolk:* Extensive infection of liver and spleen may be produced by injection of bacilli into the yolk. Trials were conducted using 6- day and 10-day embryos injected by this route. With an inoculum of 0.2 cc. of a suspension of A-27 bacilli (containing one-third of a milligram of bacilli) the embryos injected on the sixth day of incubation showed, by the twentieth day, extensive but irregular infection. Embryos injected on the tenth day with a similar inoculum showed little involvement. Although these yolk-sac experiments were repeated on three separate occasions the results were the same and were unsatisfactory. The degree of infection as manifested by lesions and bacilli in livers and spleens varied greatly from one embryo to the next. Only by the use of the intravenous route of inoculation was a sufficiently uniform infection produced in the parenchymatous organs of the embryo.

D. *Infection by intravenous injection:* This method of inoculation, utilizing the technique previously outlined, makes possible the prompt establishment of infection in the organs of the embryo. Preliminary experiments indicated the necessity for accurate control of dosage of bacilli. A series of experiments was done to determine the optimum embryo age for inoculation and the optimum dose of bacilli. Utilizing embryos of nine, ten, eleven and twelve days' incubation it was found that mortality was prohibitive when 9-day embryos were used. Later experiments have proved that embryos may be inoculated as late as the twelth day of incubation, harvested on the twentieth day, and reveal the development of lesions nearly as great in extent as those produced when inoculation occurs on the tenth day. The mortality rate is only about half as great with 12-day embryos as compared to that resulting when 10-day embryos are used.

In the determination of the optimum dose of bacilli a series of experiments was conducted in which the dose was varied over a wide range. The *volume* of the suspensions injected was uniformly 0.05 cc. The aim was to find the dose of bacilli which would regularly result in well marked infection of the livers and spleens of such degree that individual lesions would be plentiful and yet be separated by uninvolved tissue. This series of experiments involved groups of

18 embryos which received the following doses of A-27 bacilli intravenously injected on the tenth day of incubation. The livers and spleens were removed on the twentieth day and histological sections prepared.

30 bacilli 300 bacilli	No evidence of infection found.
10,000 bacilli	Occasional bacilli found in the livers. No histological changes.
30,000 bacilli	An occasional small liver lesion found in an occasional embryo.
100,000 bacilli	Regularly produced occasional small liver lesions in most of the embryos;
300,000 bacilli	Produced numerous discrete lesions in the livers varying considerably in size but usually well distributed and separated. From one or two to many large splenic lesions.
1,500,000 bacilli	This dose resulted in wide-spread infection of livers and spleens with bacilli disseminated throughout the tissues. Many confluent lesions were present.
3,000,000 bacilli	There were often wide areas of tuberculous infiltration in livers and spleens. Bacilli were widely and thickly scattered through the tissues. Liver tissue was usually degenerated and surviving embryos very small and feeble.

Further trials indicated that a range of 200,000 to 400,000 bacilli gave satisfactory results. Having determined that this dose suited the purposes of the experiments it has been used repeatedly.

When embryos are infected intravenously on the tenth day of incubation with this dose of bacilli, survivals to the twentieth day seldom exceed one-third of the injected embryos. If, however, 12-day embryos are used, and provided that the survival rate is good in opened but uninfected controls, a survival rate of 60 to 75 per cent may be expected.

Gross lesions: When embryos which had received this dose of A-27 bacilli on the twelth day were examined on the twentieth or the twenty-first day, gross lesions were found to be present in a high proportion of the spleens. The spleens were moderately to markedly enlarged. The average measurements of the normal spleen (widest diameters) are 1 x 1.5 x 1.5 mm. A glance at plate 1 will reveal the marked difference between a group of normal control spleens and a group of spleens from embryos that had received 300,000 bacilli on the twelfth day (group 3). Thus the appearance and size of the spleen serve as one rough index of infection. It was unusual to find gross lesions on the surface of the liver. Indeed it was rare that lesions of any size were immediately adjacent to the surface of the liver. Large lesions were frequently found buried within the organ but there was a margin of uninvolved tissue at the surfaces.

Gross examination of the kidney was not satisfactory because of the structure and location of the organ, but microscopic search of sections always revealed a few clumps of bacilli lying near the cortical surfaces. The cellular response in the kidney was not different in type but was always of lesser degree than in the livers and spleens.

Bacilli and lesions in the unexpanded lung were so rare that the examination of that organ was fruitless in terms of determining the degree of infection in any embryo.

On careful search, small lesions containing bacilli have been found in the submucosal connective tissue of the intestine and stomach but they do not occur regularly. Other organs have not been studied sufficiently to permit comment but no gross lesions were seen.

The spleen was always involved and offered gross evidence of infection as pointed out above. Frequently the surface was studded with many nodules. Microscopically, however, the degree of infiltration and lesion formation varied greatly from one spleen to another. Often splenic lesions were of a more advanced nature than those occurring in the liver. Thus, early necrosis at the centre of splenic lesions was common, as was giant cell formation, while both were rare in the liver. In addition to large, circumscribed, localized lesions the splenic pulp was often completely disorganized and infiltrated.

The livers of any given group of embryos regularly showed a quite uniform distribution of discrete lesions which were large enough to be readily visible under the low power microscope lens. In addition there were occasional very large lesions visible to the eye alone (figures XIII and XIV). Sometimes, within a group, an embryo was found which departed from the average degree of infection, but the liver was the organ of choice for any attempt at histologically quantitating the amount of infection present in any group of embryos.

PLATE 1

FIG. I. Chick embryo spleens removed on twentieth day of incubation and showing: controls.

Group 3—10 of a group of 13 survivors which had received 350,000 A-27 tubercle bacilli on the twelth day of incubation. The three largest spleens in the group had been used for pilot sections and are not shown.

Group 4—8 of a group of 12 survivors identical to group 3 except that 2 mg. (2,000 u) streptomycin had been administered on the twelth, fourteenth, sixteenth and eighteenth days by application to the exposed surface of the chorio-allantoic membrane.

Group 5—Survivors from a group which received streptomycin plus promin. (× ⅔)

FIG. II. Normal chick embryo liver on the fifteenth day of incubation. Note freedom from perivascular infiltration. (× 330)

FIG. III. Normal chick embryo liver on the twentieth day of incubation. Note freedom from perivascular infiltrations. (× 330)

FIG. IV. Blood island adjacent to branching vessel in a normal 20-day chick embryo liver. Such islands are composed largely of eosinophilic polymorphonuclear cells. (× 330)

FIG. V. High power view of blood island shown in figure IV. (× 1450)

FIG. VI. Section from 13-day chick embryo liver taken three days after intravenous injection of A-27 human tubercle bacilli. Occasional bacilli visible adjacent to sinusoids singly or in small packets. No cellular response. (×680)

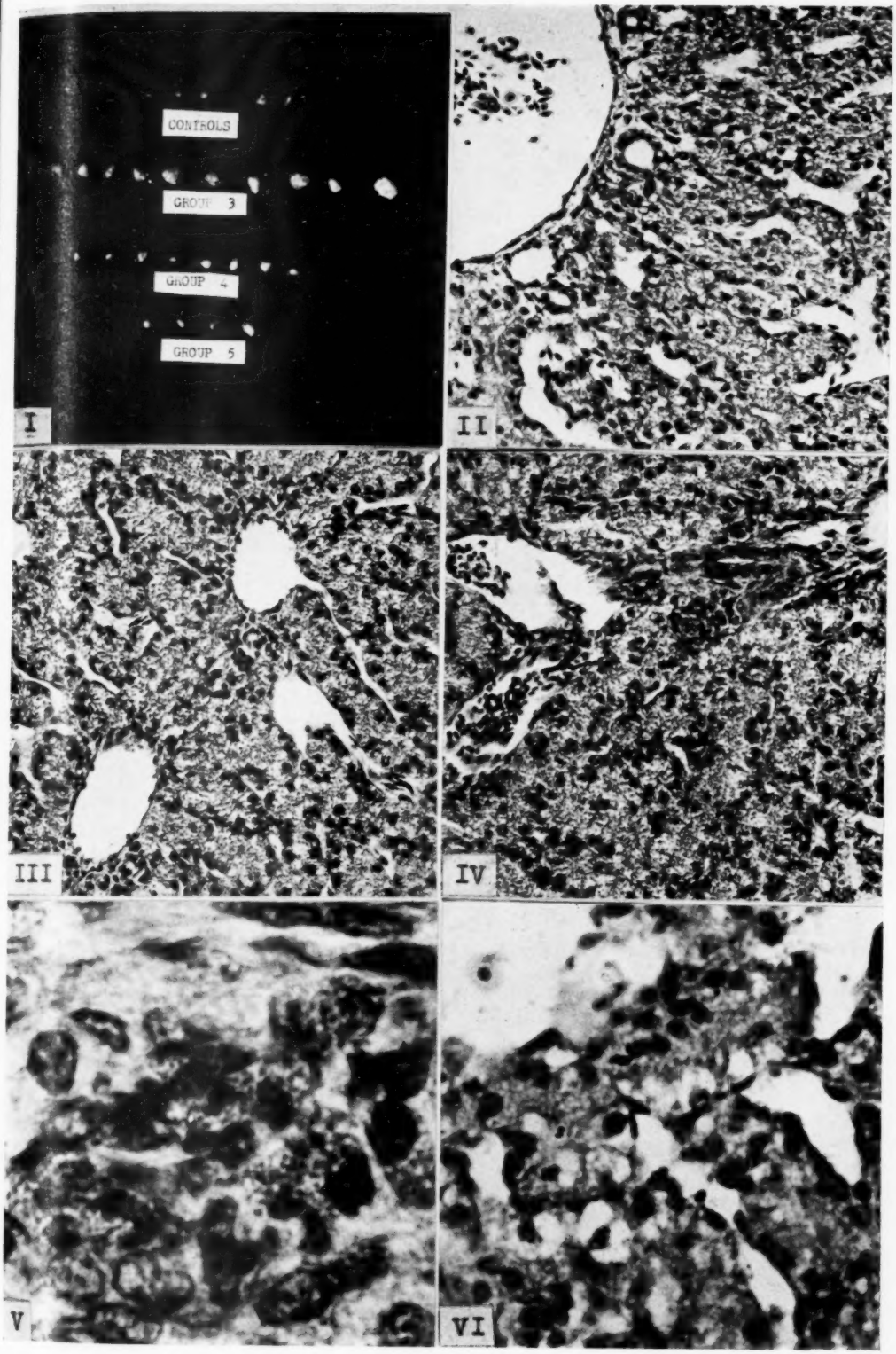


PLATE 1

Heat-killed bacilli: The injection of heat-killed bacilli by the intravenous route in the form of suspensions containing the same dose of bacilli as was used with the living organisms has repeatedly failed to produce any histological response in livers and spleens of embryos thus injected.

THE DEVELOPMENT OF INFECTION FOLLOWING INTRAVENOUS INOCULATION

In order to study the evolution of the histological changes occurring as a result of intravenous inoculation with A-27 tubercle bacilli, a group of 150 embryos were given approximately 350,000 organisms intravenously in 0.05 cc. saline. Embryos were opened and histological sections were prepared after twenty-four hours, three, five, seven and ten days. In specimens prepared twenty-four hours after infection the entire embryo was sectioned while for those prepared at the later intervals liver and spleen were examined. Tissues of at least 6 embryos were collected at each interval.

As shown in figures II and III[4] the normal embryo liver at both fifteen and twenty days' incubation is free from perivascular accumulations of cells. The liver cells are arranged in more or less regular pattern and are closely approximated to the external surfaces of all vessels. There is freedom from cellular infiltration adjacent to the walls of the large vessels, small vessels and sinusoids. Occasionally, and most often in relation to a branching vessel, a small blood island was found. The principal granulocyte of the chick is eosinophilic and it is these cells which predominate in such blood islands. Because they take the eosinophilic stain they might, under low power magnification and casual observation, be mistaken for early lesions. With a little experience or under higher magnification there is no possibility of confusion. Such an island of cells is shown in figures IV and V.

Sections of entire embryos made twenty-four hours after injection of bacilli failed to reveal any evidence of histological response and, indeed, it was only on very careful search that an occasional bacillus was found within the liver sinusoids.

After three days (figure VI) occasional individual bacilli and small clumps were found. These were usually near, but not within, the sinusoids. In most cases they did not appear to be intracellular, although in rare instances mono-

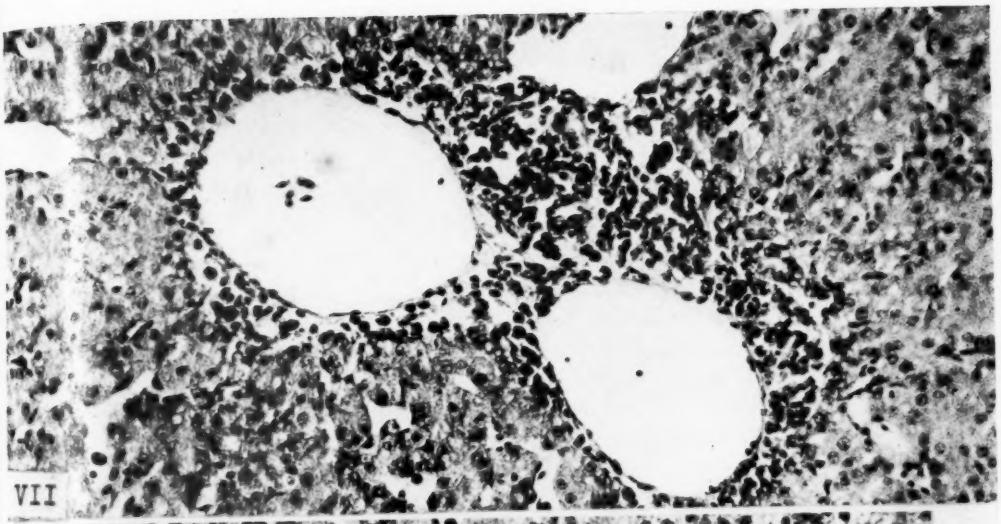
[4] All photomicrographs by Mr. B. D. Varian, Department of Anatomy, School of Medicine, University of Pennsylvania.

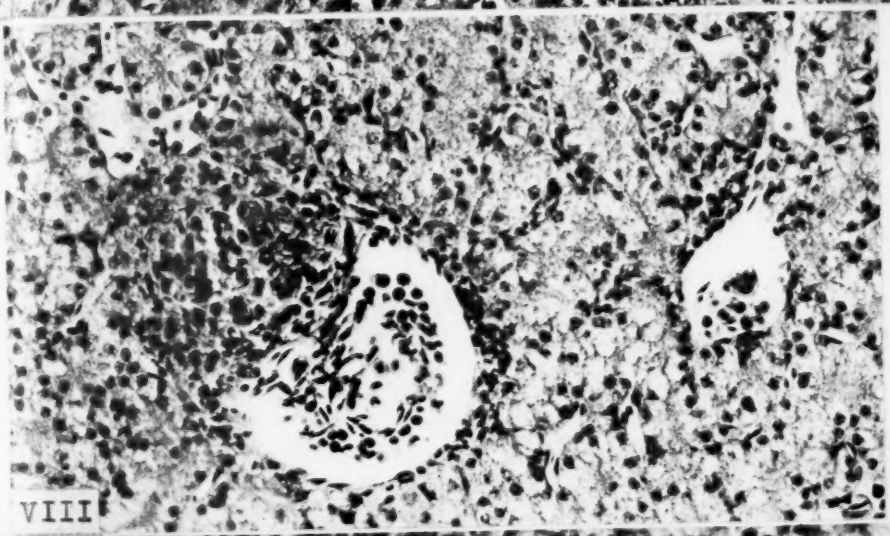
PLATE 2

FIG. VII. Section from 15-day chick embryo liver five days after intravenous injection of A-27 tubercle bacilli. Note marked perivascular infiltrations. Bacilli sparse. See text. (× 330)

FIG. VIII. Section from 20-day chick embryo liver. A small lesion is seen bulging into the vessel from which it apparently took origin. Section made ten days after injection of A-27 tubercle bacilli intravenously. Bacilli plentiful in large clumps and singly. (× 360)

FIG. IX. Part of a large elliptical lesion in a 20-day chick embryo liver ten days after intravenous injection of A-27 tubercle bacilli. Degenerating liver cells are seen at left margin. See text for discussion of histology. (× 680)





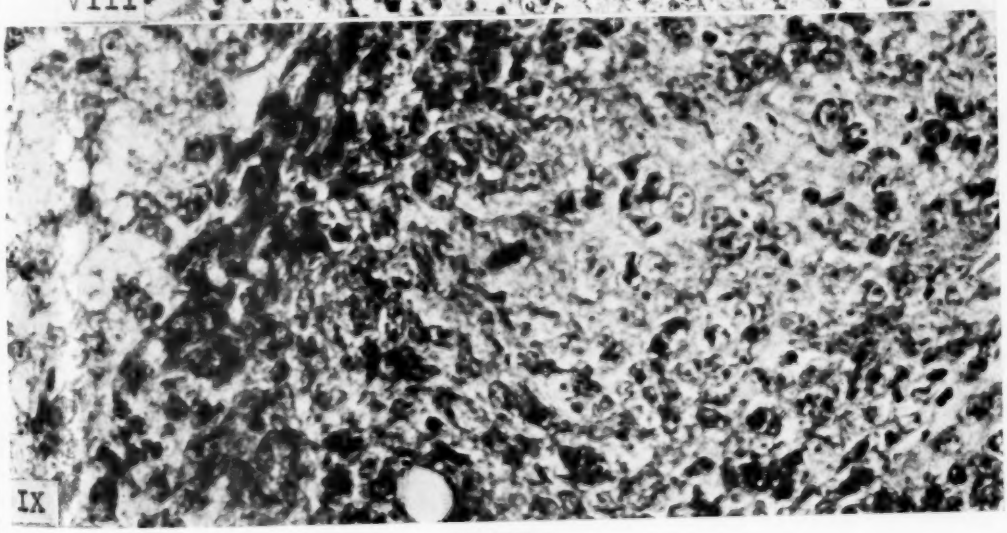


PLATE 2

nuclears were seen which contained one or more bacilli. No changes in the histological appearance of the liver were noted.

Five days after inoculation evidence of infection was well marked. Perivascular infiltrations were regularly present (figure VII). These perivascular infiltrations were composed chiefly of granulocytes but a few large mononuclear cells were also seen. At this stage the mononuclears were chiefly at the periphery of the lesions. Bacilli were still sparse but could always be found in and near the lesions under high magnification. Although occasionally intracellular the bacilli seemed to be chiefly extracellular. Sections prepared from embryos seven days after infection were unsatisfactory technically and it is not possible to derive any accurate information from them.

On the tenth day after infection the perivascular infiltrations had taken on new characteristics. Bacilli were always plentiful within the lesions being readily visible as clumps and groups of various sizes, even under low magnification. The lesions varied considerably in size but the structure of all was essentially the same. Figure VIII shows a relatively small lesion which bulged into the vessel from which it took origin. Small packets of bacilli were present. Many were intracellular. Figure IX shows part of a very large elliptical lesion. Around such large lesions there was peripheral condensation of cells to form a sort of "pyogenic membrane" or limiting wall. These peripheral cells, probably derived from the connective tissue of the liver, never contained bacilli. At this stage the central part of the lesions consisted chiefly of mononuclear cells. These mononuclears frequently contained numbers of bacilli but extracellular bacilli and clumps were also plentiful. Outside the central area of the lesions, but within the peripheral connective tissue condensation, there was a zone containing principally eosinophils although mononuclears were mixed in among them.

A higher power view of the central area of such a lesion (figure X) reveals the character of the mononuclears more clearly. Many, if not all, seemed to have a faintly reticular cytoplasm. It is quite probable that they represent young epithelioid cells.

While these liver lesions were developing, splenic lesions were also produced. As already pointed out, most spleens show gross nodules as well as microscopic lesions by the eighth day. Due to the relatively complex histology of the spleen and its extreme vascularity, the early stages of developing lesions are not as easily seen as is the case with liver lesions. After ten days the splenic

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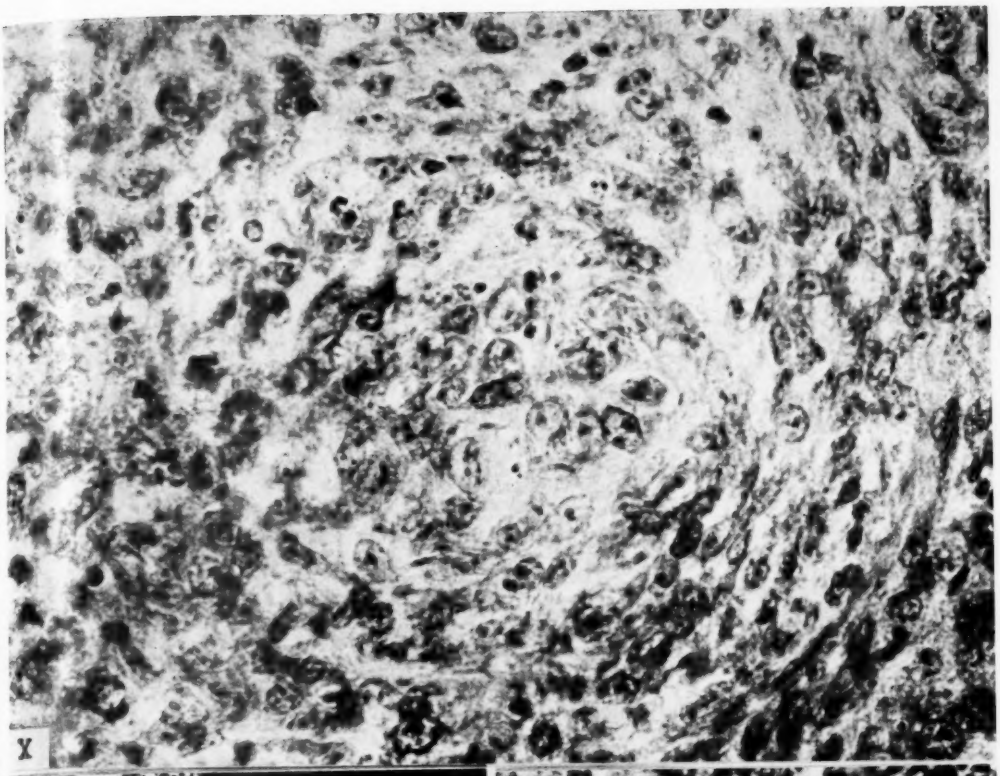
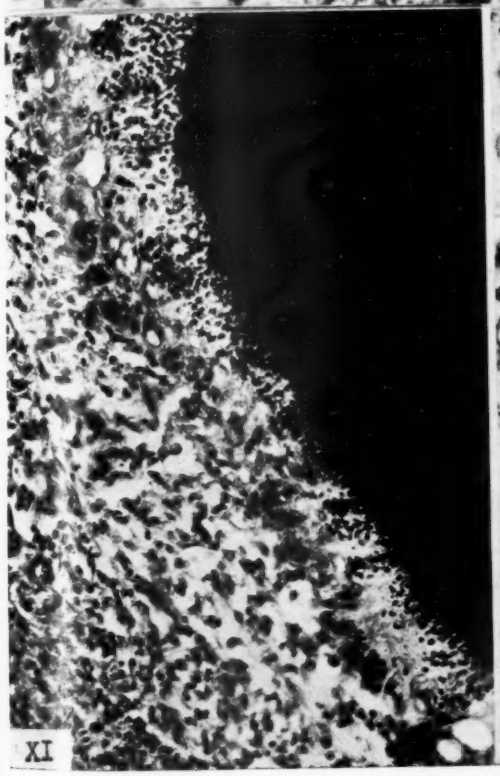
PLATE 3

FIG. X. High power view of central area of a large lesion in a 20-day chick embryo liver ten days after intravenous injection of A-27 tubercle bacilli. The character of the large mononuclear cells is apparent. Intracellular clumps of bacilli are plentiful. (× 970)

FIG. XI. Margin of a giant lesion in 20-day chick embryo spleen ten days after intravenous injection of A-27 tubercle bacilli. In the photograph the central red staining necrotic area appears solid black. (× 330)

FIG. XII. High power view of marginal giant cells of a splenic lesion in a chick emryo on the twentieth day of incubation, ten days after intravenous injection of A-27 tubercle bacilli. (× 680)





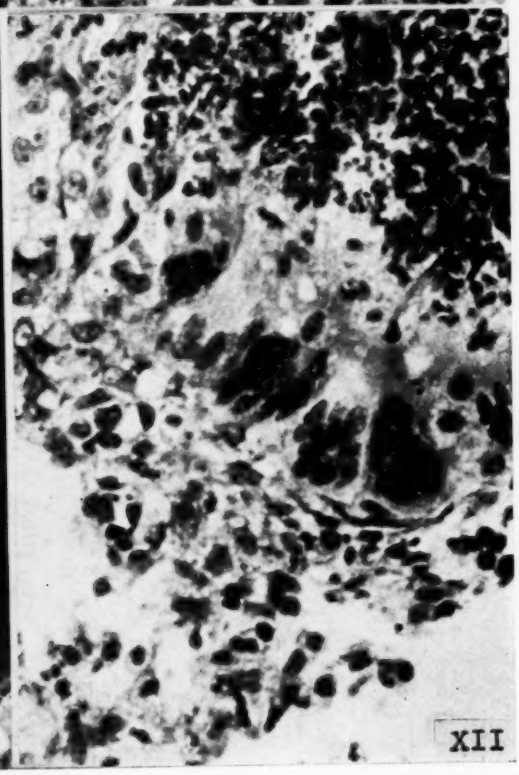


PLATE 3

lesions frequently attain a somewhat more advanced character than is usual in the liver. The margin of a giant lesion in the spleen on the tenth day after infection is shown in figure XI. The centre of the lesion, in various early stages of necrosis, took a nearly uniform dark red stain. At the margins of the area was a zone of nuclei showing pyknosis and loss of cytoplasm. Further out from the centre, intact eosinophilic polymorphonuclears and monoculears were found, while at the periphery was a margin of syncytial giant cells.

Figure XII gives a high power view of the marginal giant cells. In these large splenic lesions bacilli were constantly present but never plentiful. Many such lesions have been studied. Sometimes a single spleen is studded with them (figure I, group 3). It seems possible that the necrosis that occurs is dependent upon vascular interference by the very size of the lesion rather than

TABLE 1

Quantitative spleen cultures

Embryos infected intravenously on the tenth day with 200,000 A-27 bacilli

3 days after infection:	
	Embryo #1—200 bacilli in spleen
	Embryo #2—300 bacilli in spleen
5 days after infection:	
	Embryo #3—60,000 bacilli in spleen
	Embryo #4— 5,000 bacilli in spleen
7 days after infection:	
	Embryo #5— 4,000 bacilli in spleen
	Embryo #6—90,000 bacilli in spleen
10 days after infection:	
	Embryo #7—100,000 bacilli in spleen
	Embryo #8— 50,000 bacilli in spleen

upon the mechanisms usually producing necrosis at the centre of early tuberculous lesions. Studies are in progress concerning the effects of initial and later doses of tuberculin upon the chick embryo. There has been no definitive conclusion reached but there has been no evidence suggestive of the production of sensitization.

Within the limits of the incubation period of the embryo, this is as far as one can carry the study of the pathogenesis of these lesions. The sections shown in the photomicrographs are typical of results repeatedly produced in eight separate experiments by similar doses of the same strain of tubercle bacilli.

PLATE 4

FIGS. XIII and XIV. Low power views of sections of chick embryo livers ten days after the intravenous injection of 350,000 A-27 tubercle bacilli. Arrows mark the lesions. These two sections represent the lightest (XIII) and the heaviest (XIV) infection encountered in a group of 13 survivors. (× 36)

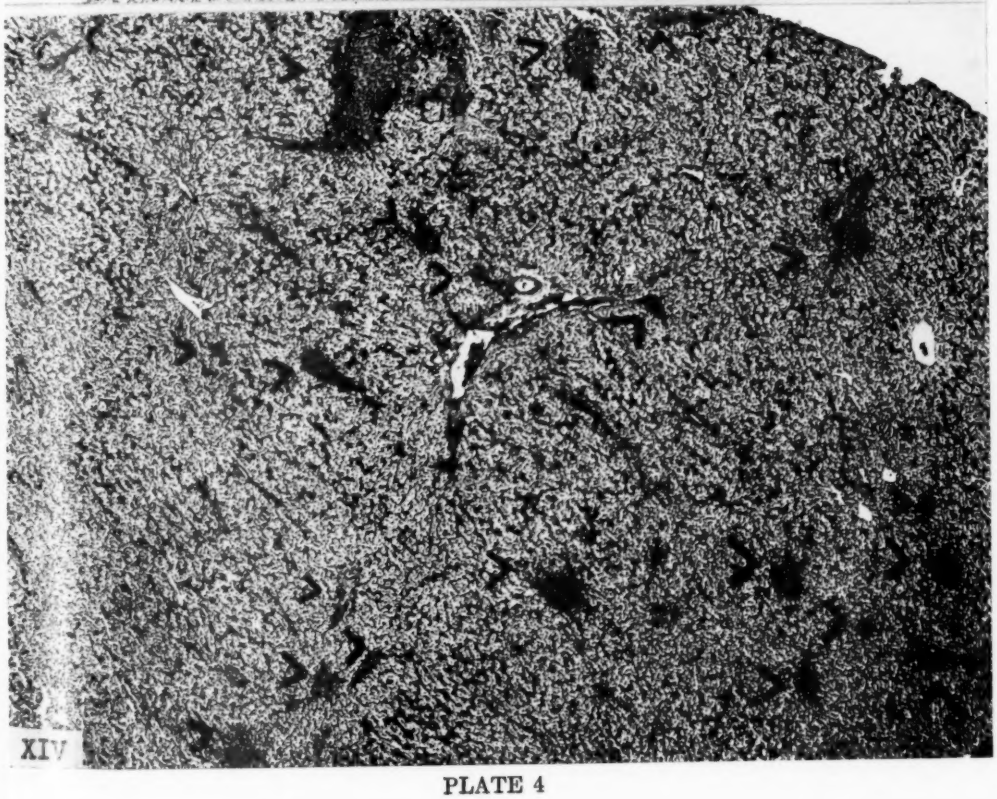


PLATE 4

These sections give ample evidence of the rapid multiplication of bacilli within the tissues. Quantitative bacterial counts made from infected spleens, while showing wide variation by the technique used, likewise gave evidence of the rapid multiplication of bacilli (table 1). These counts were made by removing the entire spleen aseptically and suspending it in a known volume of saline by prolonged trituration. Serial dilutions of the suspension of splenic tissue were then prepared and 0.3 cc. units of each suspension were plated on slants of the special media. After three weeks' incubation, colony counts were made and indicated the number of viable bacilli present in the spleen. The spleens were not weighed and no statement can be made from the data as to the bacilli present per unit weight of tissue. However, the rapid increase with the passage of time is clear.

Further evidence of the continued multiplication of the organisms was obtained by successful serial passage of A-27 tubercle bacilli through five generations of chick embryos by intravenous and yolk-sac routes of inoculation. In each instance, except for the primary inoculum, the spleen was used as the source of infection.

Trials with avian bacilli (avian-36), although limited to a single small experiment, revealed the bacilli to be chiefly intracellular. This difference in response to human and avian bacilli has been previously noted in membrane-surface experiments by Moore (1) and others (3).

USE OF THE METHOD IN TESTING COMPOUNDS FOR BACTERIOSTATIC EFFECTS

Inasmuch as a fairly uniform and predictable degree of infection can be produced, the method has been used in testing the bacteriostatic effects of several compounds including diaminodiphenyl sulfone and two new methyl derivatives, promin, diasone, furacin (5-nitro-2 furaldehyde semicarbazone) and streptomycin. Only streptomycin has given clear-cut evidence of inhibiting infection under the conditions of these experiments. With the exception of promin and streptomycin, the compounds were found to be so toxic as to preclude the use of reasonably large doses. Blood levels averaging higher than 6 mg. per 100 cc. were not obtained with the promin within the tolerated doses. The relative toxicity of various compounds for chick embryos parallels quite closely the toxicity for other animals. Detailed toxicity figures for the above compounds, except streptomycin, have been previously published (5). Streptomycin proved to be of very low toxicity for the embryo. No increase in mortality over that of controls resulted from administering 2 mg. (2,000 u) on the twelth, fourteenth, sixteenth and eighteenth days of the incubation period. The compound was administered by dropping a saline solution on the exposed chorio-

PLATE 5

FIGS. XV and XVI. Low power views of sections of chick embryo livers ten days after the intravenous injection of 350,000 A-27 tubercle bacilli followed by treatment with streptomycin applied to the exposed chorio-allantoic membrane. There were no lesions. See text. (× 36)

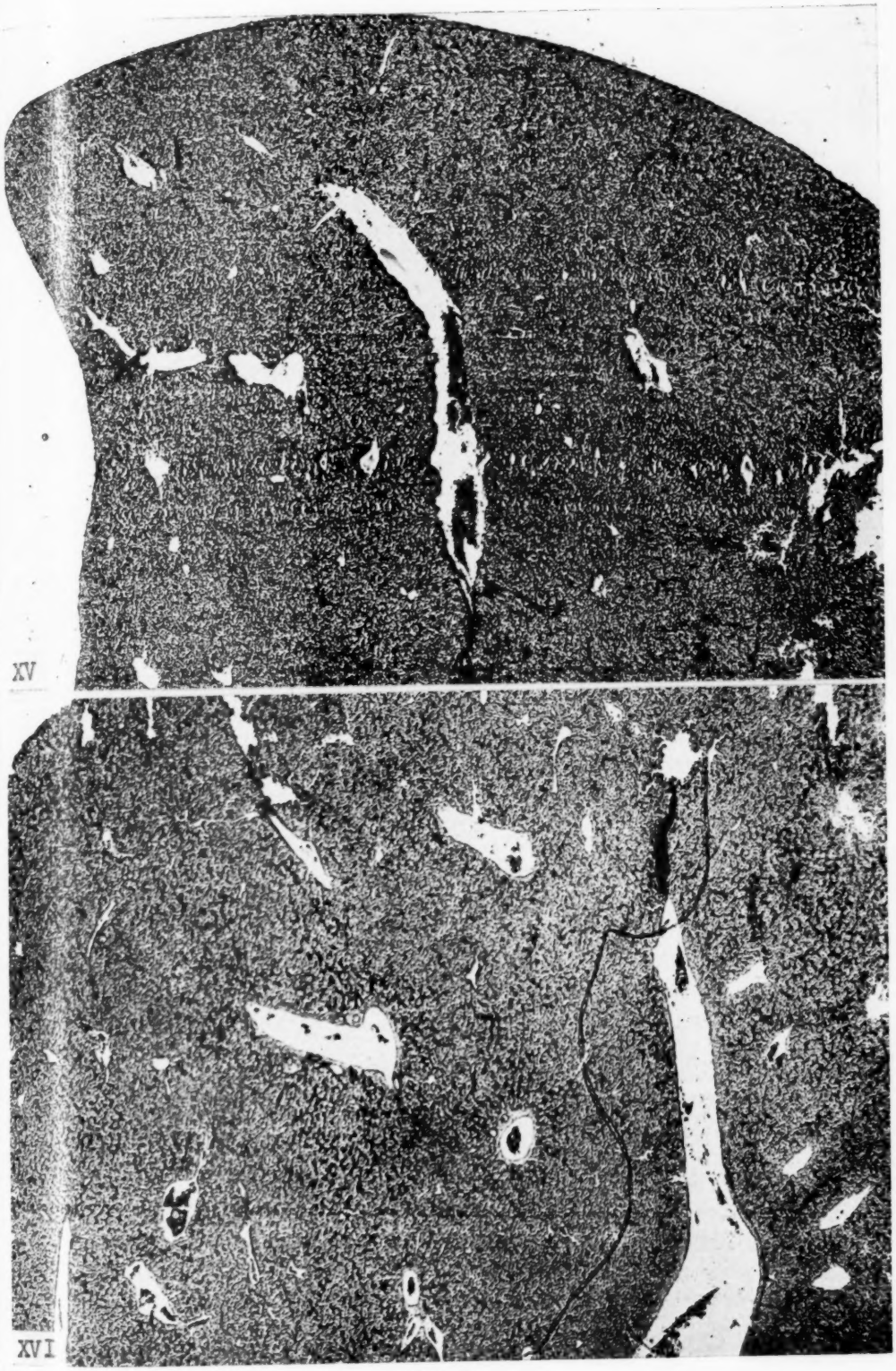


PLATE 5

allantoic membrane. Sustained blood levels of from 6 to 12 units per 100 cc. of blood were obtained with this dose.

Infection by the intravenous route with subsequent administration of the compound to be tested either by yolk-sac injection or by application to the membrane surface requires that the compound in question be delivered to the site of infection in the tissues via the blood. The choice of the membrane route or the yolk-sac route for administration of compounds depends upon the characteristics of the compound being used (5).

Table 2 outlines in condensed form one experiment in which streptomycin was used: 18 embryos, of twelve days' incubation age, were infected intravenously with a suspension of A-27 tubercle bacilli shown to contain approximately 350,000 infectious particles in each 0.05 cc. (group 3). To another group of 18 embryos similarly infected with the same suspension, streptomycin was given by the membrane-surface route immediately after the intravenous inoculation. The dose of 2 mg. (2,000 u) was contained in 0.3 cc. of physiological saline. An equal dose was also given to this group by the same route on the fourteenth, sixteenth and eighteenth days (group 4).

TABLE 2

Effect of streptomycin

12-day embryos—A-27 bacilli
Dose of bacilli approximately 350,000

Table of survivors

Embryo Age in Days	12	13	16	18	20
Group 1—Controls	18	16	16	16	14
Group 2—0.05 cc. saline intravenously	24	19	18	18	18
Group 3—Bacilli intravenously in 0.05 cc.	18	13	13	13	13
Group 4—Ditto plus 2,000 u streptomycin on membrane, stat and two, four, and six days	18	12	12	12	12

Of group 3 embryos, all but one showed: Multiple lesions (aver. 10 per section)

Of group 4 embryos, all but one showed: No lesions, no bacilli
One exception showed 20 lesions and many bacilli.

Last, a fifth group of 18, infected in the same way, received the streptomycin plus a dose of 15 mg. of promin at the time of inoculation (not included in table 2).

On the twentieth day of incubation all the embryos were harvested and the livers and spleens were removed for examination. Figure I is a photograph

showing the relative size and appearance of the spleens in the untreated infected group 3 as compared with the spleens of group 4 which received streptomycin and group 5 which received streptomycin plus promin. Those spleens from groups 3 and 4 showing the greatest degree of gross evidence of infection had been taken for sample sections before this photograph was made and thus could not be included. The sample sections revealed such a clear-cut result that the remaining livers and spleens were then sectioned.

Because of the uniformity of distribution of lesions in the liver the sections from this organ were used for histological comparisons between the groups. Sections approximately through the middle of the right lobe were prepared. The number of lesions in each liver at this location was determined. No difference was discernible between the livers from embryos receiving streptomycin alone as compared to those receiving streptomycin plus promin and the latter group has not been included in table 2. The additional toxicity of the promin resulted in the death of all but 4 embryos in the group.

The liver sections from the infected but untreated embryos revealed an average of 10 lesions per section. All these lesions were loaded with bacilli. The spleens were heavily infected. In this group with 13 survivors there was one embryo that showed no evidence of infection in liver or spleen, a result very probably due to a faulty intravenous inoculation.

Liver and spleen sections from the group infected and treated with streptomycin revealed, with a single exception, no lesions and no bacilli. One embryo revealed heavy infection in both liver and spleen. Why this one embryo of 13 survivors escaped the suppressive effect of the streptomycin is not apparent.

No stains were made for non-acid-fast forms of bacilli.

Figures XIII and XIV show low power views of liver from 2 embryos in group 3. The arrows point to lesions containing swarms of bacilli. Figures XV and XVI are of livers from the group receiving streptomycin. No lesions are present.

Cultures made from the spleens of both the treated and the untreated groups were uniformly positive although the spleens from the treated group revealed no histological evidence of infection, with the single exception already noted. These cultures were not prepared quantitatively and it is not possible to state the comparative number of organisms in the treated versus the untreated tissues.

DISCUSSION

The use of the word "tubercle" has been avoided in the presentation of this material. In the literature dealing with tuberculous infection of the chorio-allantoic membrane the word is freely used to describe the nodular infiltrations of cells produced in the mesenchyme of the membrane. There can be little objection provided the use of the word under such circumstances is clearly defined.

Burnett (9) has discussed the rather nonspecific response of chick embryos to various irritants. Pandit (12) reported on the histological lesions produced in the membrane by different bacteria, by alumina gel and by other foreign substances. In our laboratory the intentional inoculation of the membrane with a mold has produced a histological picture nearly indistinguishable from that produced by inoculation with human tubercle bacilli except, of course, for the

absence of bacilli in the lesions. This nonspecificity of response on the part of the embryonic membrane tissue should be kept in mind when tubercles are discussed.

Likewise caution should be observed in the interpretation of the term caseation or "caseation necrosis." These terms are in use as descriptive of the central necrosis occurring in the lesions produced in the membrane by tubercle bacilli. As pointed out in a previous section of this paper, necrosis has been encountered in the spleens of infected embryos. It has seemed to us that this has been associated with circulatory derangement and, indeed, swarms of erythrocyte nuclei are usually seen in such areas of necrosis both in spleens and in membrane lesions. If the term "caseation necrosis" implies the response of tuberculin-sensitized tissue there is at least no factual evidence to support it in the embryo. If it simply implies necrosis from other causes it is certainly permissible.

We have no evidence as to the specificity or lack of specificity of the lesions produced by the intravenous inoculation of tubercle bacilli. The important fact is that the tubercle bacilli of the strain used do produce an easily recognized type of histological response and that one chemical substance, streptomycin, was able to prevent the development of the infection. Further studies concerned with the possible presence of non-acid-fast forms of bacilli, quantitative bacterial tissue cultures and the fate of the infection in embryos carried beyond the incubation period are suggested by the results obtained.

Previous chick embryo tests for the tuberculostatic effects of various substances have been confined to implantation of bacilli upon the exposed chorioallantoic membrane and the concomitant or subsequent application of the substance to be tested to the same area. It is believed that the method here presented offers certain advantages in that the substances tested and the inoculum of bacilli are completely separated and the compound must therefore reach the site of developing infection via the blood-stream. Also, by the method described, infection is produced within the living parenchymatous organs. It is obvious that embryonic tissue is not adult tissue and that such a method does not replace the necessity for testing promising compounds in other animals. However, with the use of this method, testing is accomplished under the conditions imposed by living organs with intact cell barriers and enzyme systems.

In so far as has been determined, the chick embryo does not produce antibodies during the incubation period and therefore one variable present in more mature tissue is absent in the embryo.

Chick embryos are relatively inexpensive. A large number of infected individuals can be handled and kept in a small space. From the date of inoculation to the finished histological sections requires a time interval of less than three weeks if proper facilities are available. For all the above reasons it is believed that the method here reported offers a technique of potential value as a screening procedure in chemotherapeutic research.

SUMMARY

Intravenous inoculation of chick embryos with a human strain of tubercle bacilli (A-27) results in the prompt establishment of infection within the paren-

chymatous organs. The histological picture produced has been presented. With proper dosage of bacilli the uniformity of distribution of lesions within the liver makes possible quantitative evaluation of the degree of infection in any given group of embryos. This method may serve as a screening procedure in chemotherapeutic research. The validity of the method was sustained in trials with streptomycin which was found to prevent the development of histological evidence of infection. Despite the absence of visible bacilli or histological response in streptomycin-treated embryos, viable bacilli were recovered from the organs in large numbers by cultural methods.

SUMARIO

La inyección intravenosa de los embriones de pollo con una cepa de bacilos humanos (A-27) da por resultado el rápido establecimiento de la infección en los órganos parenquimatosos. Descríbese el cuadro histológico evocado. Con una dosis apropiada de bacilos, la distribución uniforme de las lesiones intrahepáticas permite la avaluación cuantitativa de la intensidad de la infección en cualquier grupo dado de embriones. Esta técnica puede servir para la eliminación en la investigación quimioterapéutica. La validez de la misma quedó comprobada en las pruebas ejecutadas con estreptomicina la cual, según se observó, impidió la aparición de signos histológicos de infección. A pesar de la ausencia de bacilos visibles o de respuesta histológica en los embriones tratados con estreptomicina, se obtuvieron grandes cantidades de bacilos viables de los órganos por medio de las técnicas de cultivo.

Acknowledgments

We wish to express our thanks to Dr. Max B. Lurie of the Henry Phipps Institute and to Dr. Eugene Opie for their suggestions and for their help in reviewing the sections.

These studies were carried out in laboratory space provided by the Henry Phipps Institute, Philadelphia, Pennsylvania.

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EFFECT OF STREPTOMYCIN ON THE TUBERCLE BACILLUS[1,2]

The Use of Dubos' and Other Media in Tests for Streptomycin Sensitivity

EMANUEL WOLINSKY AND WILLIAM STEENKEN, JR.

This study was undertaken to compare the different methods of performing streptomycin sensitivity tests, and especially to evaluate the usefulness of the new liquid medium of Dubos (7, 8).

The *in vitro* inhibition of growth of the tubercle bacillus by streptomycin was first described by Schatz, Bugie, and Waksman (1), and has since been studied by Waksman and his coworkers (2, 3), Youmans (4), Smith and McClosky (5), and Emmart (6). The sensitivity of several strains of tubercle bacilli, as determined in or on various types of fluid synthetic media, has been reported by these authors to be from 0.2 units of streptomycin per cc. of medium for partial inhibition of growth, to 1.5 units per cc. for complete inhibition.

Materials and methods: The sensitivity tests were performed by three methods: (*1*) surface growth on synthetic medium; (*2*) deep-seated growth in synthetic medium; (*3*) in Dubos' liquid medium. The effects of streptomycin on the virulent human strain, H37 Rv only, will be considered in this paper. Proskauer and Beck's fluid synthetic medium at pH 7.2 to 7.4 was used. The Dubos medium was made up as described by Dubos and Davis (7), and dispensed in 5 cc. amounts in test tubes. The streptomycin[3] was in the form of the hydrochloride. The organisms to be tested in Dubos' medium were first transferred from fluid synthetic or solid media by triturating with a platinum spade a small amount of growth on the side of the tube containing Dubos' medium. The organisms grew homogeneously, and thereafter could be carried by serial transfer in Dubos' medium. With large inocula, growth of H37 Rv could usually be detected in three days, with maximum turbidity in ten to twelve days. After several transfers in Dubos' medium, growth was sufficiently smooth and diffuse, after shaking the tube, to give reliable turbidimetric readings in a photoelectric colorimeter.

Sensitivity tests by surface growth on synthetic medium: Twenty cc. of Proskauer and Beck's fluid synthetic medium were dispensed in flat, 100 cc. bottles and autoclaved at 10 lbs. pressure for twenty minutes. Streptomycin was added to give concentrations of 0.05, 0.2, 0.4, 0.6, 0.8, and 1.0 micrograms[4] per cc. Each concentration, as well as the control medium without the drug, was represented by three bottles. A 10 by 10 mm. loopful of H37 Rv microörganisms from

[1] From the Research and Clinical Laboratory, Trudeau Sanatorium, Trudeau, New York.

[2] Brief mention of some of this work was made in the discussion of Feldman and Hinshaw's paper on streptomycin treatment of experimental tuberculosis, presented at the 42nd annual meeting of the National Tuberculosis Association, Buffalo, New York, June 12, 1946.

[3] Streptomycin hydrochloride, lot 165, was kindly supplied by Merck and Company through the courtesy of Doctors Carlisle and Robertson.

[4] The newer quantitiative expression of streptomycin is by weight of pure streptomycin base. One microgram is equivalent to one S unit.

an actively growing pellicle on synthetic medium was floated on the surface of the medium in each bottle. Comparison of the surface growth was made by visual estimation, and measurement of the size of the pellicle, at various intervals of incubation. After twenty-one days the organisms were harvested by filtering on silk. They were then removed from the silk, and dried and weighed in porcelain crucibles. The pellicle measurements proved to be grossly inaccurate and difficult to evaluate because of the tendency of the pellicle to disperse, and at times to grow very dense in certain areas.

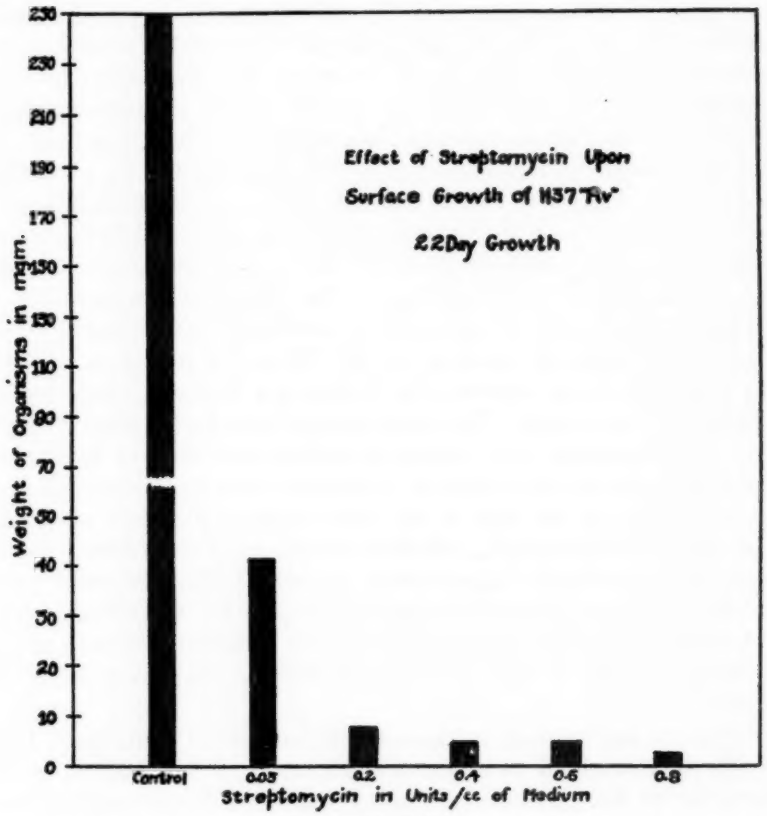

CHART 1

Note: One S unit of streptomycin (pure base) is equivalent to one microgram.

Chart 1 shows the weights of surface growth obtained; each bar represents the combined weights of growths from three bottles. One 10 by 10 mm. loopful transferred a pellicle of about 2 to 4 mg. dry weight of microörganisms. The control bottles gave a growth of 250 mg. Streptomycin in concentration of 0.05 micrograms per cc. reduced this growth to 41.7 mg., 0.2 micrograms per cc. allowed only 7.6 mg. of growth, and 0.4 to 1.0 micrograms per cc. gave a harvest of 1.5 to 2.8 mg., which represents complete inhibition of growth.

Sensitivity tests by deep-seated growth in synthetic medium: Youmans and his

coworkers (4, 9) have been using this method to test the streptomycin sensitivity and acquired resistance of tubercle bacilli. He reported that, using an inoculum of 0.1 mg. and an incubation time of fourteen days, 0.19 to 0.78 units of streptomycin per cc. inhibited the growth of H37 Rv; 0.78 units per cc., according to Youmans, was also able to completely inhibit inocula of 0.5 mg. and 1.0 mg.

Proskauer and Beck's fluid synthetic medium was dispensed in 10 cc. amounts in 20 by 150 mm. test tubes and autoclaved at 10 lbs. pressure for twenty minutes. Enough streptomycin was then added to give concentrations of 0.05 to 2.0 micrograms per cc. In each series, there were five control tubes without streptomycin and three tubes for each concentration of the drug. A suspension of organisms to be inoculated was prepared by triturating a rapidly growing pellicle in a mortar with a small amount of saline (10). A known volume of this suspension was then evaporated on a weighed watch glass and the number of mg. dry weight of microörganisms per cc. determined. Into each tube a known weight of organisms was pipetted. The tubes were then sealed with paraffin, and a small air hole was probed through the paraffin plugs. The tubes were incubated at 37°C.

The results were quite irregular. On two occasions, once with an inoculum of 0.1 mg. and once with 0.15 mg. for each tube, none of the controls showed any growth. Often, there was growth in only one or two of the three tubes at a given concentration of streptomycin. Growth was usually first evident in the control tubes in five days, and reached a maximum in sixteen days. The organisms grew in the form of small, discrete clumps at the bottom of the tube. After a variable time, if growth continued to progress, a surface pellicle would form.

The results of a typical experiment are shown in table 1. The inoculum was 0.2 mg. of H37 Rv in each tube. After sixteen days of incubation, a concentration of 0.4 micrograms of streptomycin per cc. was sufficient to inhibit growth, but, as the incubation time increased, tubes containing higher concentrations of streptomycin began to show growth. Thus, after twenty-two days, 0.8 micrograms per cc. was necessary for inhibition, and after thirty-eight days, one out of three tubes containing 1.0 microgram per cc. showed growth. After thirty-eight days and up to fifty-five days of incubation, none of the tubes showed initial growth.

Sensitivity tests in Dubos' medium: Enough streptomycin was added to tubes containing Dubos' medium to give concentrations of 0.05, 0.1, 0.2, 0.4, 0.6, 0.8 and 1.0 micrograms per cc., and each tube, as well as a control tube without streptomycin, was inoculated with 0.1 cc. of a growing culture (eight to ten days old) of H37 Rv microörganisms in Dubos' medium. The final volume in each tube was 5 cc. Growth was estimated by visual turbidity at intervals after incubation at 37°C. Results are presented in table 2.

From table 2 it will be noted that growth was first observed in the control tube and the tube containing 0.05 micrograms per cc. in three days, reaching a maximum in about twelve days. With 0.1 microgram, there was very slight turbidity noted in four days. The turbidity remained minimal until the four-

teenth day, after which it showed progressive increase up to twenty days. With 0.2 micrograms, turbidity was first noted on the fourteenth day, and it did not show progressive increase until the twentieth day. The tube containing 0.4 micrograms remained clear for twenty days, then showed a rapidly increasing

TABLE 1

Effect of streptomycin on growth of H37 Rv: Deep-seated growth in Proskauer and Beck's fluid synthetic medium at pH 7. 2: Inoculum 0. 2 mg.

STREPTOMYCIN IN MICROGRAMS PER CC.	TUBE NUMBER	DAYS OF INCUBATION AT 37° C.				
		5	16	22	38	55
0 (controls)	1	+	4+	4+	4+	4+
	2	+	4+	4+	4+	4+
	3	+	4+	4+	4+	4+
	4	+	4+	4+	4+	4+
	5	0	4+	4+	4+	4+
0.1	1	+	4+	4+	4+	4+
	2	+	4+	4+	4+	4+
	3	0	3+	4+	4+	4+
0.2	1	0	+	2+	4+	4+
	2	0	+	2+	4+	4+
	3	0	0	+	4+	4+
0.4	1	0	0	+	3+	4+
	2	0	0	+	3+	4+
	3	0	0	+	3+	4+
0.6	1	0	0	+	2+	2+
	2	0	0	+	2+	2+
	3	0	0	+	3+	3+
0.8	1	0	0	0	2+	3+
	2	0	0	0	+	2+
	3	0	0	0	+	2+
1.0	1	0	0	0	+	+
	2	0	0	0	0	+
	3	0	0	0	0	+
1.5	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	0	0	0	0

0 = no growth; + = very slight growth; 4+ = maximum growth.

turbidity up to twenty-eight days. Tubes with 0.6 micrograms per cc. showed complete inhibition of growth of the organisms within the period of observation, twenty-eight days.

The effect of streptomycin on H37 Rv microörganisms grown in Dubos' medium

can be shown more accurately and graphically if growth turbidity is measured in the Klett-Summerson photoelectric colorimeter, using the following procedure: To tubes containing 10 cc. of Dubos' liquid medium, various amounts of streptomycin were added to give concentrations of 0.05 to 1.0 micrograms per cc. A control tube without the drug was included. The tubes were inoculated with 0.1 cc. of an actively growing six-day culture of H37 Rv in Dubos' medium, and the contents of each tube distributed in 5 cc. amounts into two Klett tubes, giving duplicate cultures for each concentration of streptomycin. The inoculum for each Klett tube was calculated to be 0.001 mg. dry weight of H37 Rv, or about three million organisms. Using the number 54 green filter, colorimeter readings for each tube were made immediately upon inoculation, and at one- or two-day intervals during incubation. The tubes were plugged with lightly paraffined cotton containing a small air hole.

One or two tubes of plain Dubos medium were included in each series. The colorimeter was first brought to zero with the plain medium, then each inoculated

TABLE 2

Effect of streptomycin on growth of H37 Rv in Dubos' liquid medium at pH 7.1

STREPTOMYCIN IN MICROGRAMS PER CC.	DAYS OF INCUBATION AT 37° C.									
	3	4	5	7	11	14	17	20	23	28
0 (control)	+	2+	2+	3+	4+	4+	4+	4+	4+	4+
0.05	+	2+	2+	3+	4+	4+	4+	4+	4+	4+
0.1	0	+	+	+	+	2+	3+	4+	4+	4+
0.2	0	0	0	0	0	+	+	2+	3+	4+
0.4	0	0	0	0	0	0	0	0	2+	3+
0.6	0	0	0	0	0	0	0	0	0	0
1.0	0	0	0	0	0	0	0	0	0	0

0 = no growth; + = very slight turbidity; 4+ = maximum turbidity.

tube was read in turn against this control. To convert the colorimeter reading to weight of organisms in mg. per cc., the reading was multiplied by the factor, 0.004, which was derived as follows: 0.2 cc. of an actively growing culture of H37 Rv microörganisms in Dubos' medium was inoculated into 45 cc. of Dubos' medium in a flask. After nine days of incubation at 37° C., a turbidimetric reading was made in the Klett-Summerson colorimeter, which gave a dial reading of 52. Exactly 15 cc. of this culture was passed through a previously weighed sintered glass, ultra fine, bacteriological filter, through which tubercle bacilli could not pass. The organisms were washed several times with distilled water, and dried to constant weight. For example, 3.6 mg. dry weight of microörganisms were obtained in this way from the 15 cc. of medium, or 0.24 mg. per cc.; 0.24 divided by the dial reading, 52, gave the factor of 0.0046. The average of several such determinations was 0.004.

The results of a typical experiment are presented in chart 2.

In chart 2 the dial readings of the Klett-Summerson colorimeter, and the

calculated weights of organisms for each reading, are plotted against the time of incubation in days. Each point represents the average reading of the two tubes. It may be seen that the control tubes showed evidence of increasing turbidity by the second day. From the second to the sixth day there was a period of rapid logarithmic growth, followed by a ten-day period of less rapid logarithmic growth. Streptomycin in concentration of 0.1 microgram per cc. produced noticeable inhibition of growth for twelve days, after which the inhibitory action was broken through, and the growth curve ascended rapidly.

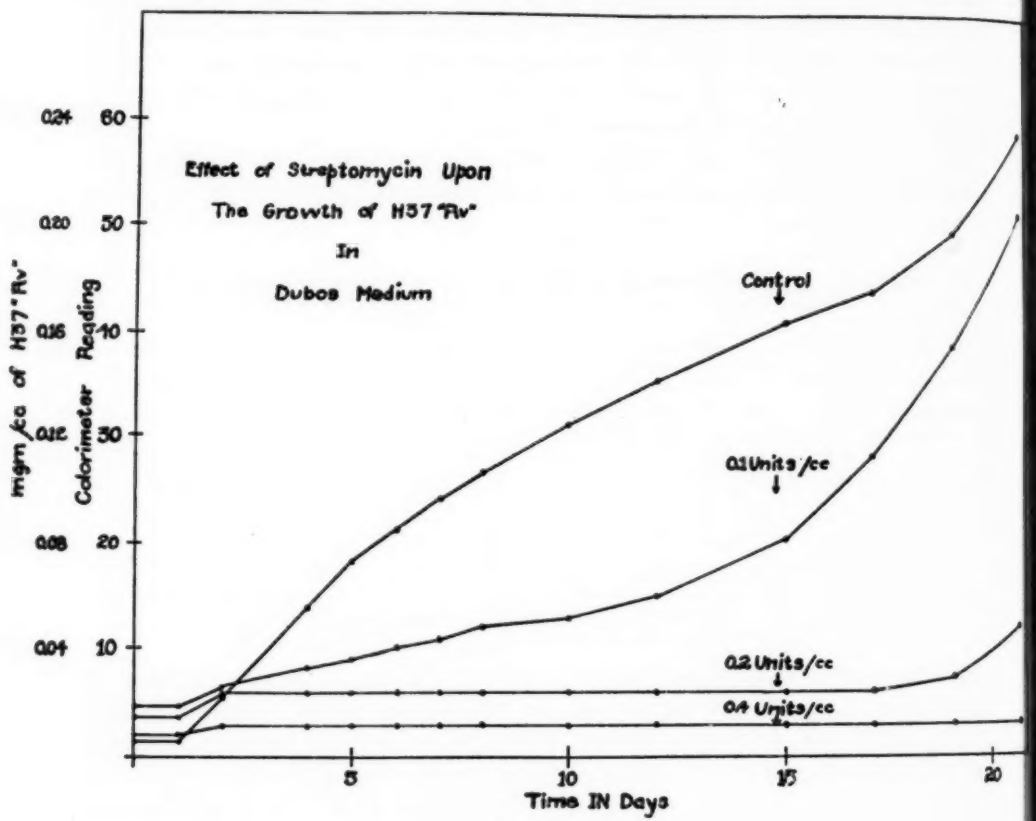

CHART 2

Note: One S unit of streptomycin (pure base) is equivalent to one microgram.

With 0.2 micrograms per cc., there was no evidence of growth for seventeen days, then the appearance of growth turbidity, which increased rapidly to the twenty-first day. Streptomycin in concentrations of 0.3 micrograms per cc. and higher produced complete inhibition of growth for twenty-one days.

DISCUSSION

The foregoing results indicate that approximately the same concentration of streptomycin is necessary to inhibit the growth of H37 Rv, whether tested in

Dubos' medium, in Proskauer and Beck's synthetic medium by surface growth, or in Proskauer and Beck's medium by subsurface growth, provided the pH of the medium is kept between 7.1 and 7.4. It is obvious that the time of incubation is an important consideration, as the longer one waits before taking the final reading, the more streptomycin will be recorded as the inhibiting concentration. It is suggested that the period of observation of growth of the sensitivity tests be limited to a few days over the time necessary for maximum growth of the controls without the antibiotic agent. In any case, the incubation time and the pH of the medium should always be mentioned when recording the sensitivity of an organism.

Of the three methods presented, the one which makes use of the Dubos medium is by far the best for streptomycin sensitivity tests of tubercle bacilli, in that it is more rapid and less cumberson than the other methods. Other antibiotic agents may be tested just as readily, provided they are not inhibited by any of the constituents of the medium. Testing by surface growth on synthetic medium is unwieldy. If the pellicle tends to disperse, measurement is inaccurate. The more reliable method of weighing the resulting growth after a fixed period of observation is a delicate and time-consuming operation. Deep-seated growth in Proskauer and Beck's synthetic medium has proved to be highly unpredictable in our hands, when compared with the Dubos medium method.

Using comparable inocula (attained by using 0.1 cc. of Dubos' medium cultures of about the same age and turbidity), essentially the same results for sensitivity of H37 Rv to streptomycin in Dubos' medium were obtained on four different trials. It is more rapid than the other methods, the end points are distinct, the results fairly constant and the effect of the drug on the growth of the organism can be studied quantitatively by turbidimetric measurements in the Klett-Summerson photoelectric colorimeter. A definite idea of the sensitivity of an organism may be obtained in four or five days, as increasing turbidity can be noted by this time. Final readings may be made in fourteen to twenty days.

SUMMARY

1. The effect of streptomycin on the growth of the human type of tubercle bacillus, H37 Rv, was tested by three different methods.

2. The method utilizing the new liquid medium of Dubos was found to be the most satisfactory.

3. Streptomycin in concentration of 0.05 micrograms per cc. was found to inhibit growth of H37 Rv slightly, 0.2 micrograms per cc. to inhibit growth markedly, and 0.4 micrograms per cc. to inhibit growth completely, with an incubation time of sixteen to twenty days in media at pH 7.1 to 7.4.

SUMARIO

1. El efecto de la estreptomicina sobre el crecimiento del tipo humano del bacilo tuberculoso H37Rv, fué comprobado con tres técnicas distintas.

2. La técnica que resultó más satisfactoria fué la que utiliza el nuevo medio líquido de Dubos.

3. La estreptomicina a la concentración de 0.05 microgramos por cc. inhibió levemente el crecimiento del H37Rv, a razón de 0.2 microgramos por cc. lo inhibió decididamente y a razón de 0.4 microgramos por cc. lo inhibió completamente con un tiempo de incubación de doce a veinte días en medios con un pH de 7.1 a 7.4.

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Paul Pressly McCain
1884–1946

Dr. Paul McCain's life touched so many other lives, his professional skill brought healing to so many patients, his wisdom made his opinions so valuable to his colleagues, and his lovable disposition grappled so many friends to his soul with hoops of steel that it is hard to realize he is no longer with us in the flesh. The newspapers told the story of his untimely death, the result of a collision with a bus on the morning of November 25, 1946. Death struck with merciful swift-

Paul Pressly McCain
1884-1946

ness, and it is probable that he was spared any suffering. He himself would surely have chosen to go while in the full possession of his splendid mental faculties, and would have wanted to be useful to the very last.

The bare outline of Paul McCain's life is to be found in *Who's Who*. He was born in Due West, South Carolina, on June 26, 1884. He received his B.A. degree from Erskine College in 1906, and his M.D. degree from the University

of Maryland in 1911. In 1936 the University of North Carolina honored him with the LL.D. degree. After a year's internship at Bay View Hospital, Baltimore, and a two years' residency at Gaylord Farm Sanatorium, he came to the North Carolina Sanatorium as chief of medical service and assistant superintendent in 1914. Here he spent the rest of his life. In 1917 he married Sadie Lou McBrayer, whose father was then superintendent of the Sanatorium, and in 1924 he succeeded Doctor McBrayer as superintendent. In 1936 the Western North Carolina Sanatorium at Black Mountain, and in 1941 the Eastern Branch at Wilson were added to his responsibility.

The honors which have come to Doctor McCain have come unsought, and bear testimony to his worth. He was a Diplomate of the American Board of Internal Medicine and a Fellow of the American College of Physicians. In 1935 he was president of the Medical Society of the State of North Carolina. In his chosen field of tuberculosis he has been signally recognized, having been president of both the Southern Tuberculosis Conference and the National Tuberculosis Association. He has been a member of the Editorial Board of the *North Carolina Medical Journal* from its beginning in 1940, and was the first chairman of the board.

This outline does not tell of the man himself. Many times it has been said that if a vote were taken to select the best loved doctor in North Carolina, Paul McCain would be overwhelmingly chosen. Another measure of his worth is the fact that, during the thirty-two years he held public office, no one ever questioned his integrity, his ability or his judgment.

Doctor McCain is survived by his widow and four children, two of whom are following in his footsteps as disciples of the healing art.

WINGATE M. JOHNSON

BOOKS

W. A. D. ANDERSON: *Synopsis of Pathology. Second Edition. Pp. 741, with 327 text illustrations and 15 color plates, C. V. Mosby Co., St. Louis, 1946.*

By DAVID A. WOOD

In a strict sense this book of 741 pages is neither a synopsis nor a textbook. The author has brought forth a book with a tremendous amount of condensed information which should be useful to general practitioners as a supplement to standard textbooks. It is a book, however, which in the opinion of the reviewer is unsuited for undergraduate students. Of necessity, the attempt to present pathology in a synopsis has in a number of instances resulted in not only sketchy and incomplete, but dogmatic presentations. An example is seen in Chapter 3 where embolism of tumor cells is discussed. It is stated that "embolism of tumor cells is one of the chief methods of which malignant tumors spread, with the formation of new or metastatic tumors in distant organs. Vein walls are more easily penetrated by invading tumor cells than are arteries. Hence tumor embolism is mainly venous, and spread is most frequently to liver and lungs." In this chapter the importance of lymph vessel permeation and embolism in carcinoma is completely ignored. An uninformed reader would conclude from the sketchy presentation that the rule is for metastasis to occur by way of blood vessel dissemination.

Dogmatism is apparent in the chapter on tuberculosis. On the other hand, the chapter on rickettsial and viral diseases is quite good, although short. Discussion of histoplasmosis, toxoplasmosis, and mycotic infections is brief but good. Chapter 10 on chemical poisons deals with the subject quite superficially. It omits almost completely any reference as to the mechanisms of action. The author fails to emphasize that it is absorbed poison which is of importance, and, therefore, it is paramount that portions of the liver and kidney, with other pertinent tissues, be collected along with stomach and gastric contents for toxicological examination. In discussing cyanide poisoning, no mention is made concerning the mechanism of action (interference with oxidation), merely—"hydrocyanic acid and cyanides cause very rapid death, leaving diagnostic morphologic changes. The characteristic odor of peach kernel or bitter almonds assists in detecting the poison."

The subject of oncology is presented quite well. The author adheres in places to the older histological classification, using such terms as undifferentiated sarcoma, small round cell sarcoma, large round cell sarcoma, mixed (polymorphic) cell sarcoma, and spindle cell sarcoma. Teratoma of the mediastinum is not specifically mentioned. A broad definition of cyst is used to include "a cavity containing fluid and surrounded by a definite wall. There is usually an epithelial lining." With such a broad definition he includes as cysts those spaces which "arise by outpouchings from bursae and tendon sheaths (e.g. ganglion)."

As a whole, Chapter 13 on kidneys, urinary tract, and male genitalia is well

written. Possibly greater emphasis should be placed on the fact that lipoid nephrosis is a degenerative phase of latent glomerulonephritis. In discussing malignant renal tumors, the author states that there are two main types, (*1*) "renal carcinoma or hypernephroma (Grawitz tumor)" and (*2*) "embryonal adenosarcoma (Wilms' tumor)." He regards hypernephromata as simply renal carcinomata, but does discuss briefly the histogenetic aspects of possible adrenal rest origin for some. Accordingly, he considers the clinical behavior of hypernephromata and renal carcinomata as similar.

Discussion of Mikulicz's syndrome offers another example of dogmatic presentation—"a bilateral enlargement of the parotid glands, sometime with an involvement of other salivary glands and lacrimal glands. It may be of inflammatory origin (tuberculosis, sarcoid, etc.), or be due to leukemic infiltration or to Hodgkins' disease." It would be more correct to state that the etiology is unknown.

This book with its wealth of material, in spite of its superficial and dogmatic passages, should be valuable to the person who has already completed his undergraduate study of pathology. With a few exceptions the color plates are as good as can be expected. The text illustrations are well diversified and selected.

Brief Comment

Tuberculosis in the United States, Graphic Presentation, Volume 4. Mortality Statistics for Urban Places and Rural Areas in each County, 1939–41. Prepared by the Staff of the Field Studies Section of the Tuberculosis Control Division, U. S. Public Health Service, under the direction of Carroll E. Palmer, M.D. Medical Research Committee, National Tuberculosis Association, 1946. Pp. vii + 190, paper.

"The volumes of this series, *Tuberculosis in the United States, Graphic Presentation*, are the result of a cooperative undertaking by the National Tuberculosis Association and the U. S. Public Health Service. The basic data were made available by the U. S. Bureau of the Census."

"The present volume gives the tuberculosis mortality record for the counties of each State, their urban places of 10,000 or more population, and rural areas for the 1939–41 period. Since health activities are usually organized on a county or multi-county basis, the presentation of tuberculosis mortality by counties makes available in easily accessible form the data necessary for more complete understanding of local tuberculosis mortality situations.

"The mortality data in this volume are based upon the place of residence of the decedents. Statistics by race, when shown, are presented in two classifications: white and nonwhite. The latter group consists in large part of Negroes (about 95 per cent) and includes Indians, Chinese, Japanese, and others of nonwhite races. Mexicans are included with 'white.'

"Mortality statistics are available by race for the counties, urban places, and rural areas of each State in which five or more per cent of the population outside cities of over 100,000 is nonwhite, or if the nonwhite population outside those cities is 100,000 or more. In addition, a race division is made for cities of over 100,000 in which the nonwhite population constitutes at least 10 per cent of the total population or numbers at least 20,000. Following these rules, statistics by race are presented for the urban places and rural areas of the counties of 22 States and for 12 cities of over 100,000 population in other States. For the remaining counties, urban places, and rural areas, tuberculosis mortality data are shown for all races only."

"The present volume presents a table and a map for the United States and for each State. The table shown for the United States contains, for 1940, basic data on population, deaths from tuberculosis (all forms), and death rates for tuberculosis by race and sex for population groupings of various size. The table shown for each State contains, for the period 1939–41, basic data on population, deaths from tuberculosis, and death rates for tuberculosis by race where available for each county, urban place, and rural area. For the United States and for each State a map is shown in which the tuberculosis death rates for all counties of 10,000 or more population have been classified into four groups or quartiles. The counties were ranked in ascending order according to their mortality rates; the lowest one-fourth of the counties were grouped as the first quartile, the next highest one-fourth as the second quartile, and so on. Each of these groups of counties is distinctively marked to demonstrate the distribution of the areas of different tuberculosis mortality. Quartile grouping of the county tuberculosis mortality rates for the white and nonwhite populations is likewise shown in maps for each of the States where a race breakdown is available. It should be pointed out that comparisons cannot be made between maps in this volume for the quartile groupings for each State are based on the distribution of mortality rates in that State alone.

"Knowledge of the location of tuberculosis sanatoria and mental hospitals is necessary since a large number of tuberculosis deaths occur among the patients in such institutions. Deaths in such institutions of patients who have been resident therein for over one year are allocated to the county in which the institution is situated, resulting in a considerable increase in the tuberculosis mortality of these counties. Therefore, symbols designating the location of Federal and State tuberculosis sanatoria and mental hospitals have been placed on the State maps."

"Reprints of the tables and maps for individual States are available and may be obtained without charge from the Tuberculosis Control Division of the U. S. Public Health Service. These may be assembled along with others from the previous volumes of this series into 'State volumes.' It is suggested that those interested in the subject assemble reprints for their own State, as well as for neighboring States or geographic divisions which they may wish to include for comparison." [From the Foreword]

BCG VACCINATION

Plans of the United States Public Health Service

On September 7, 1946 a conference on BCG vaccination was held in the offices of the Tuberculosis Control Division of the U. S. Public Health Service in Washington, D. C. The members attending the conference were Dr. J. Burns Amberson, College of Physicians and Surgeons, Columbia University, New York; Dr. Joseph D. Aronson, Henry Phipps Institute, Philadelphia; Dr. Howard W. Bosworth, Barlow Sanatorium, Los Angeles; Dr. Charles A. Doan, College of Medicine, Ohio State University, Columbus, Ohio; Dr. Johannes Holm, State Serum Institute, Copenhagen, Denmark; Dr. Esmond R. Long, Henry Phipps Institute, Philadelphia; Dr. Jay A. Myers, University of Minnesota, Minneapolis; Dr. David T. Smith, Duke University, Durham, N. C.; Dr. Henry Stuart Willis, William H. Maybury Sanatorium, Northville, Mich.; and Dr. I. C. Yuan, National Institute of Health, Nanking, China.

The Public Health Service was represented by Doctors Herman E. Hilleboe and Carroll E. Palmer of the Tuberculosis Control Division, and Dr. Milton V. Veldee, Biologics Control Laboratory of the National Institute of Health, Washington, D. C.

A brief review of the past experience with BCG vaccination was presented by the Chief of the Tuberculosis Control Division with detailed discussion of the work in South America.

During the conference, the studies of Dr. Aronson and his coworkers were presented by Dr. Aronson and discussed by Dr. Carroll E. Palmer, who assisted in the analysis of these data.

Dr. Johannes Holm presented his investigations and those of his coworkers in Denmark which have been carried on since 1930. After a detailed discussion of the material presented by Dr. Aronson and Dr. Holm, there was a general discussion of the whole problem of BCG vaccination, including the experimental work done on the relationship between allergy and immunity in tuberculosis.

Dr. Veldee presented the problems of virulence and stability of vaccine which contains live organisms. Dr. Veldee also discussed the need for more research before commercial licensing of BCG vaccine can be considered.

As the result of these deliberations of outstanding leaders in tuberculosis in the United States, China and Denmark, certain recommendations were made, which will be used as a guide in the expansion of the research program of the Tuberculosis Control Division of the United States Public Health Service.

It was strongly urged that BCG vaccine should not be commercially produced at present in the United States. Extensive investigations are indicated before commercial distribution can be considered. Upon the detailed review of the literature and the presentations of the members of the conference, it was concluded that BCG vaccination appears to confer increased resistance to tuberculosis, for the period of time covered in the studies. At present, however, information is incomplete as to the degree of this resistance or its duration.

Neither do these studies as yet answer the question of the long-time effect of BCG vaccination on aging members of the population.

On the basis of a careful review of all published reports and the experience of members of the conference who have actually done vaccination, it was agreed that there have been no proved cases of progressive disease from BCG vaccination in human beings.

Vaccination of human beings with BCG vaccine can be done without causing severe local reactions at the site of injection or in the regional lymph nodes, provided that proper vaccine, dosage and method of administration be used. It was recommended that the intracutaneous method of vaccination be utilized in any studies contemplated. Further research should be done in the other methods of vaccination, in an attempt to develop some technique to decrease the number of severe local reactions to the vaccine.

It was agreed that properly prepared BCG vaccine could convert a high percentage of nonreactors into reactors to tuberculin. There is as yet no conclusive information concerning the duration of tuberculin sensitivity which results from BCG vaccination. In order to study the need for revaccination of those reactors who become nonreactors after vaccination, it was recommended that one study group be revaccinated and another group not be revaccinated, so that the need for revaccination might be determined.

It was recommended that a single laboratory produce BCG vaccine for the whole country during the period of the proposed expanded study program and that this laboratory be established and supervised by the United States Public Health Service. It was recommended that conferences be held with representatives of France, Scandanavia, South America and China, in order to work out plans for uniform methods of producing BCG vaccine and for a comparison of the vaccine strains used in different countries of the world. Coöperative planning of studies should also be undertaken.

It was recommended that investigations be carried on during the coming year on certain population groups in the United States, in order to determine the effectiveness of this vaccine in the control of tuberculosis. Persons exposed to such a degree that they are almost certain to become infected, should be given first consideration. Particularly should we concern ourselves with the various tribes of American Indians in the United States, inmates and employees of mental institutions, employees of general hospitals and sanatoria where the danger of infection is excessive because control measures are lacking, medical students in schools where the services include exposure to tuberculous patients, and persons economically and socially underprivileged, among whom tuberculosis mortality is very high. It is not recommended that the vaccine be used in areas, such as Minnesota, where the incidence of tuberculosis and the percentage of tuberculin reactors is markedly low. Extensive studies in populous areas should be initiated by the Public Health Service in coöperation with local groups. It was suggested that a county or part of a State, with a population of at least 100,000 people, could be studied over a period of several years in order to determine the effect of BCG vaccination on an entire community.

Other local groups which would agree on the method of selection of the sample and the controls, and on the methods of study and analysis, could be furnished vaccine free by the Public Health Service. It was recommended that the vaccine not be furnished to general practitioners for use in individual patients at this time.

CONCLUSIONS AND RECOMMENDATIONS

1. BCG vaccine should not be made commercially available at present.
2. From studies presented at the conference, it appears that BCG vaccination confers increased resistance to tuberculosis for the limited period of time covered in these studies.
3. Medical literature fails to reveal any proved cases of progressive disease as a result of BCG vaccination.
4. BCG vaccination can be done without causing severe local reactions.
5. The intracutaneous method of vaccination is recommended for use at present.
6. In the studies presented, BCG vaccination converted a large percentage of nonreactors (to the tuberculin test) into reactors.
7. Need for revaccination and time interval between vaccination require further study.
8. It was recommended that a single laboratory be established by the Tuberculosis Control Division to produce BCG vaccine for the whole country for use in research programs proposed at this conference.
9. Extensive investigations should be carried on coöperatively with recognized research groups throughout the country during the coming years, especially in population groups highly exposed to tuberculous infection.
10. It was recommended that the Tuberculosis Control Division set up a controlled study in a community containing 100,000 or more people, to determine immediate and long-range results.
11. Further research is strongly recommended to determine the efficiency of the vaccination and also to attempt to develop a vaccine composed of dead bacilli. It was recommended that methods be developed to standardize techniques of preparation of a potent and stable vaccine for use in the United States and if possible throughout the world.

This policy was approved by Surgeon General Thomas Parran on October 7, 1946.

HERMAN E. HILLEBOE, Medical Director
Chief, Tuberculosis Control Division

NOTICE

United States Public Health Service

Fellowships for Physicians and Engineers

Announcement is made by Surgeon General Thomas Parran of the U. S. Public Health Service that applications for Fellowships in post-graduate public health training for physicians and engineers for the school year beginning in the fall of 1947 will be received at any time prior to May 1, 1947.

The Fellowships are made possible by a grant of $228,400 from the National Foundation for Infantile Paralysis through funds contributed to its March of Dimes. Fifty-three students were awarded Fellowships for the school year beginning in September, 1946.

The Fellowships provide an academic year's graduate training of approximately nine months in an accredited school of public health or an acceptable school of sanitary engineering followed by three months of field training, and are open to men and women, citizens of the United States, under 45 years of age. Physician applicants must have completed at least a year's interneship. Engineering graduates with a Bachelor's or higher degree in Sanitary, Civil or Chemical Engineering are eligible; and those with other engineering degrees who have had experience in the public health or sanitary engineering field may also submit applications. The Fellowships are administered by the Committee on Training of Public Health Personnel, which consists of representatives of schools of public health, the State and Territorial Health Officers, the American Public Health Association, and the U. S. Public Health Service.

The specific purpose of the Fellowships is to aid in the recruitment of trained health officers, directors of special services, and engineers to help fill hundreds of vacancies existing in State and local health departments throughout the country. The Fellowships are intended for newcomers to the public health field, and are not open to employees of State and local health departments, for whom Federal grant-in-aid funds are already available to the States.

Applicants for Fellowships may secure further details by writing to the Surgeon General, U. S. Public Health Service, 19th and Constitution Avenue, N. W., Washington 25, D. C., Attention Public Health Training.

NOTICE

Excerpta Medica

Excerpta Medica will be the collective title of some fifteen periodicals containing abstracts of medical publications, shortly to be published periodically. These journals will give, as completely as possible, a survey of the world's medical literature. All these abstract journals will be in the English language.

Fifteen separate abstract journals will be published by *Amsterdamsche Boek- en Courant Maatschappy*, Amsterdam, Holland, under the editorship of Prof. Dr. A. P. H. A. de Kleyn, Prof. Dr. M. W. Woerdeman and Prof. Dr. W. P. C. Zeeman. The fifteen Sections, which can be obtained separately, will appear monthly, or if necessary bimonthly, and will be devoted to the following topics:

Section I: Anatomy, Embryology, Histology
Section II: Physiology, Biochemistry and Pharmacology
Section III: Endocrinology
Section IV: Microbiology and Hygiene
Section V: General Pathology and Pathological Anatomy
Section VI: Internal Diseases (also Infectious Diseases)
Section VII: Pediatrics
Section VIII: Neurology and Psychiatrics
Section IX: Surgery (also Orthopedics and Urology)
Section X: Obstetrics and Gynecology
Section XI: Oto-, Rhino-, Laryngology
Section XII: Ophthalmology
Section XIII: Dermatology and Venereology
Section XIV: Radiology
Section XV: Tuberculosis

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NOTICE

British Commonwealth and Empire Health and Tuberculosis Conference —July 8 to 10, 1947

A Conference on Tuberculosis, arranged by the National Association for the Prevention of Tuberculosis of Great Britain, will be held in London from July 8th to 10th inclusive. There will be special reference to the problem as affecting the British Commonwealth, and representatives from all the Dominions and Colonies have been invited, but the Conference will deal with tuberculosis in all its aspects, and it is hoped to welcome many visitors from other countries.

The Rt. Hon. Aneurin Bevan M.P., Minister of Health, has promised to attend on the first day of the meeting, and to speak on the subject of Tuberculosis and the National Health Service Act.

The sessions will include discussions on Tuberculosis in the British Commonwealth and the Colonial Tuberculosis Services; sanatorium design; after-care and rehabilitation; the psychology of tuberculosis; new discoveries in the prevention and treatment of the disease; and the National Health Service and its effect on tuberculosis schemes.

Plans are being made for overseas guests to see something of the antituberculosis work for which Great Britain is famous, and will include visits to sanatoria, hospitals and clinics, and demonstrations of various kinds. The Conference is open to both doctors and laymen, from this country and from overseas, and fuller particulars can be obtained from the Secretary-General, National Association for the Prevention of Tuberculosis, Tavistock House North, Tavistock Square, London, W.C.1.

THE INTERNATIONAL UNION AGAINST TUBERCULOSIS

KENDALL EMERSON[1]

Control of epidemic diseases has been a matter of international concern for centuries. Quarantine was and still is the official protective measure employed. While not perfect, it plays a large part in circumscribing sporadic outbreaks of the more virulent infections. Prior to the recent war the Public Health Division of the League of Nations at Geneva maintained a statistical bureau which received daily cables from stations throughout the world, reporting all cases of diseases such as cholera, yellow fever, plague, typhus and the like. This enabled the quarantine principle to reach a high level of efficiency.

Tuberculosis, the most wide-spread of communicable diseases, has profited little from the application of this principle and that only in very recent years. Migration of the tuberculous is still but mildly impeded by national regulations or international agreements. The reasons for this contrast between tuberculosis and the more swiftly lethal pestilences need not detain us. Sir Robert Philip's teaching that control of tuberculosis is a responsibility of the people summarizes the situation. Cholera and yellow fever dramatize themselves and lead to instant popular demand for governmental action. Not so with the insidious attack of the *Mycobacterium tuberculosis*. Here health education must be invoked, based on interchange of world experience and research.

In the "Nineties" Germany recognized this need. The Central International Bureau for the Prevention of Consumption was organized in Berlin. This was the forerunner of the present International Union, although the latter was organized *de novo* after the first world war, subsequent to a refusal on the part of England, France and The U.S.A. to continue their memberships in that organization, which then passed out of existence. It is not unfair to state, however, that this original organization with its biennial international conferences had demonstrated the value of such an agency.

Preliminary discussions looking toward the development of an International Union against Tuberculosis arose during a meeting of the National Association for the Prevention of Tuberculosis in London in the autumn of 1919. Our delegates to that meeting were Dr. Charles J. Hatfield, Dr. David R. Lyman and Dr. William Charles White, while Dr. Leon Bernard and Dr. Edouard Rist represented France. Subsequent conferences with Sir Robert Philip and with M. Léon Bourgeois, who had been Chairman of the extinct International Conference on Tuberculosis, led to an agreement that Mr. Bourgeois should send formal invitations to the national tuberculosis associations of England, France, Italy and the United States to appoint delegates to an organization meeting in Paris in 1920.

This meeting took place, the United States being represented by a number of

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physicians and laymen. Organization of an International Union against Tuberculosis was completed and a constitution adopted, providing for the election of officers, a directing Council and an Executive Committee. The Council has representatives from each of the member states of the Union and the Executive Committee consists of not less than five elected members. Council members from the United States were Drs. James Alexander Miller, Gerald B. Webb, David R. Lyman, George E. Bushnell and Charles L. Minor. Dr. Webb was made a member of the Executive Committee. He was followed successively in that office by Dr. Farrand, Dr. Hatfield, Dr. Theobald Smith, Dr. E. L. Opie and the present Managing Director of our Association.

Such, in bare outline, was the origin of the International Union against Tuberculosis. It grew out of the conviction that an unofficial scientific body would be able, through periodic informal conferences, to advance world interest in tuberculosis research and the promotion of preventive measures for the control of this disease. In 1926, at the Washington Conference, the barriers preventing former enemy countries to adhere were withdrawn. Membership increased rapidly until at the outbreak of the second world war 44 countries or colonies were represented. Certain of these have voluntary associations like our own which represent their respective states. Others have associations partly subsidized by government and still others, having no such agencies, are represented by delegates appointed from the tuberculosis control divisions of their public health departments. The Union, however, retains the independent status of a voluntary group with its own constitution and elected officers and issues the transactions of its conferences as the unofficial consensus of scientists from many countries with primary interest in tuberculosis research and control.

The last conference held was at Lisbon in 1937. Unrest in the Iberian Peninsula made travel through Spain undesirable and the delegates gathered at Havre and took ship for Lisbon. This was an agreeable arrangement as it gave time for preliminary discussions, the renewal of old acquaintanceships and the formation of new ones. In Portugal it was decided to hold the 1939 conference in Berlin. The second world war broke out three days before the date scheduled for the meeting. Through the foresight of our State Department no delegates were appointed to represent this country, thus escaping the uncomfortable situation in which those from certain other countries found themselves.

The effect of the war on the International Union was grave but not disastrous. The office was visited by Germans during the years of occupation and while activities were interdicted its library and records were not disturbed. No communication with the outside world was permitted and until 1945 no direct word was received from its Secretary General, Dr. Bezançon, or its executive secretary Dr. Alix Churchill. The last number of the Union's Quarterly Review was issued in January, 1940. This publication, in addition to news and scientific comment, summarized the tuberculosis statistics of the numerous countries holding membership. Access to, or publication of such figures was prohibited during the period of German occupation. This has proved most baffling in any attempt to secure reliable statements on the effect of war conditions on tuberculosis morbidity and mortality, especially in countries which suffered most

from active fighting. It is well known, however, that in areas occupied by the Germans organized public health work languished pitiably. Tuberculosis sanatoria were looted, destroyed or used for other purposes. Patients were discharged with little provision made for their care. In many cases they were put to work. New foci of infection were thus spread through many regions with cynical disregard of patient or community welfare.

After the cessation of hostilities in 1945 immediate interest arose as to the future status of the International Union. The chaos in Europe, difficulties in the matter of transportation and even communication delayed action for more than a year. Furthermore, organization of the United Nations presented a new relationship which required careful thought. It seemed wise to await the result of plans for the World Health Organization which were taking shape under Section IX, Economic and Social Welfare of the United Nations Charter. This was a sound decision since relations have been established with the Interim Committee, under Dr. Chisholm's direction, of most satisfactory promise.

Finally on November 7, 1946, the Executive Committee of the International Union met at its Paris office, 66 Blvd. Saint Michel, at the call of the Secretary General. Representatives were present from Poland, Norway, Belgium, Portugal, England, France and the United States. The last elected President of the Union, Dr. Lopo de Carvalho of Portugal, presided. The Secretary General reported on the difficulties under which the Union had maintained its office during the five years of German occupation. Income from constituent members was wholly lacking. The French Government had made a generous contribution which enabled the continuance of a skeleton staff on reduced salaries. All publication and outside communication was impossible. No material damage had been suffered in the office. Dr. Bezançon then introduced the non-members of the Committee who had been invited to attend, among them Dr. Parisot, liaison officer appointed by Dr. Chisholm, General Secretary of the World Health Organization's Interim Committee.

Dr. de Carvalho welcomed the group and spoke of the persisting need of such an agency as the Union under existing world health conditions. He also confirmed a rumor that the Germans had proceeded with the meeting of the Union called for September, 1939, that with only Axis representatives present new officers had been elected and the Union taken over by the Germans. He told of a visit to Portugal made by a representative of this rump organization who called upon him and attempted to gain his approval of the action taken in Berlin. Dr. de Carvalho flatly refused, stating that he himself would remain in office until his successor was duly elected by a body truly representative of the Union.

Before discussing future plans the United States delegate on the Executive Committee begged leave to introduce the following resolution for the consideration of the members:

"On behalf of the International Union against Tuberculosis, the Executive Committee in formal session at the Headquarters of the Union, 66 Boulevard St-Michel, Paris, November 7, 1946, respectfully presents the following resolu-

tion to the Interim Commission, World Health Organization of the United Nations:

I—*Whereas*, it is recognized that, due to war and post-war conditions, tuberculosis has greatly increased in many regions and threatens to become a world-wide epidemic of serious proportions, and

II—*Whereas*, the International Union against Tuberculosis believes that, to combat this menace to public health throughout the world, the strongest possible organization of national and international resources is essential.

III—*Therefore*, be it resolved that the International Union against Tuberculosis respectfully suggests to the Interim Commission that it give serious consideration to the establishment and maintenance of a strong Division of Tuberculosis within its services, with a competent staff of experts in the Administration of Tuberculosis Control, to promote the development of a coöperative program among Member Nations to combat this disease."

Dr. Parisot, delegated by the World Health Organization (United Nations) to represent it at the Executive Committee of the International Union against Tuberculosis, declared, on behalf of this Organization, that "the latter is willing to establish with the International Union against Tuberculosis a very close collaboration, whether on the scientific plan or (if the Union so wishes) on the administrative plan: for instance, it would place at the disposal of the Union an Office near the seat of the World Health Organization, its staff, its library etc.... The Organization wishes to specify that, in proposing this, it does not intend to diminish in any way the autonomy of the International Union against Tuberculosis whose strength is based on its private character and independence, while on the other hand, it considers that a close collaboration between the Executive Committee of the Union and the Secretariate of the World Health Organization would be to their mutual advantage."

After translation, the two documents were unanimously approved by the Committee and the Executive Secretary was directed to acquaint Dr. Chisholm with this action.

The question of when and where the next international conference should be held was then raised. It was pointed out that the Council of the Union had the responsibility of making a decision on these matters. The Secretary General was then empowered to call a meeting of the Council for this purpose. July of 1947 was decided upon as an appropriate time for such a meeting. This will come after the June meeting of the World Health Organization which is expected to come into full existence at that time. We will then be in an advantageous position to clarify more definitely our relations with that body.

The Council will concern itself chiefly with matters of reorganization, the election of officers, suggested amendments to the present constitution of the Union and a discussion of plans for the next conference which will probably take place in some European country during 1948 or 1949. It has been customary for the members to devote a half day to discussion of some scientific topic. Streptomycin was suggested as an appropriate subject for consideration at the forthcoming meeting.

Finally, the Executive Secretary was asked to resume correspondence as soon as possible with all states adherent to the Union reporting the meeting of the Executive Committee and inviting participation on the part of old members in the forthcoming meeting of the Council.

A pleasant interlude in the day's work was a most agreeable luncheon for the Committee Members and guests at the *Cercle Interalliée* provided by Dr. Bezançon. The club occupies one of the most charming residences on the *Faubourg St. Honoré* with gardens running down toward the *Champs Élysées* and is doubtless familiar to many who may read this account. A number of distinguished French physicians were asked to join us, among them Drs. Poix, Guérin, Édouard Rist and Étienne Bernard. Needless to remark, the food was in the French manner of perfection and the wines of choicest vintage.

The future of the International Union against Tuberculosis under the new political organization of the world will present a number of puzzling problems. The Interim Commission of the World Health Organization has indicated its interest in a strong international voluntary association and expressed its belief that such a non-official agency can be of assistance in a collaborative relationship. This should mean the inclusion, as nearly as possible, of all countries in the membership of the Union.

From the functional point of view it would appear that regional groups might well be established along the lines suggested by the Interim Commission. This would require expansion of the organizational and administrative responsibilities of the central office and would necessitate more liberal financing than in the past.

Again the character of the biennial conferences should receive most careful consideration, having in mind especially social and economic as well as scientific factors which influence the control of tuberculosis. Such questions will come up for consideration at the time of the forthcoming Council meeting and much preliminary thought should be put into the planning of this meeting and preparation of agenda covering essential points for discussion.

PNEUMOPERITONEUM IN THE TREATMENT OF PULMONARY TUBERCULOSIS[1]

Results in 710 Cases from 1937 to 1946

ROGER S. MITCHELL,[2] JOSEPH S. HIATT, JR.,[3] PAUL P. McCAIN,[4] HERMAN F. EASOM[5] AND CHARLES D. THOMAS[6]

Artificial pneumoperitoneum has been used to treat pulmonary tuberculosis at the North Carolina Sanatorium since 1937 and at the Eastern North Carolina Sanatorium since its opening in 1943, with increasing frequency and success. Of the 710 patients who have received pneumoperitoneum at some time during their residence, 474 were so treated for three months or longer; it is upon the latter group, in which pneumoperitoneum has ostensibly been given a sufficient trial, that this report is based. The complications cover the entire 710 cases.

REVIEW OF THE LITERATURE

Since artificial pneumoperitoneum was first used to treat pulmonary tuberculosis by Vadja in 1933 (87), after a suggestion made by Banyai (5) in 1931, to be followed by the latter's persistence since 1934 (6 to 21), so little time has elasped that comprehensive studies on large series of cases over sufficiently long periods of time have been virtually impossible.

Table 1 is a chronological summary of the reports from all sources which give any results of pneumoperitoneum treatment for pulmonary tuberculosis. Of the 58 reports, 18 cover 5 cases or less and 36 cover 50 cases or less, while 22 reports are based upon a maximum period of observation of one year or less.

Recently, however, several reports cover over 100 cases each, for periods of observation of up to four and five years (3, 35, 36, 73). It is of interest that these late reports are favorable, and one is enthusiastic enough to predict that pneumoperitoneum plus diaphragmatic paralysis will mark a greater advance in the treatment of pulmonary tuberculosis than the advent of artificial pneumothorax (36).

Not more than 8 reports can be considered unfavorable to pneumoperitoneum (39, 42, 58, 75, 76, 83, 84, 85). Three of these by one author, Trimble (83, 84, 85), are offset by his most recent, favorable, opinion (86). Of the other 5 unfavorable reports, the largest is a series of 50 cases (42), and the longest maximum period of observation is two years (39).

A great many of the papers on pneumoperitoneum, especially those of the pioneer Banyai, unfortunately merely review its history, technique, indications

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[2] Present address: Trudeau, New York.
[3] Sanatorium, North Carolina.
[4] Died November 25, 1946.
[5] Wilson, North Carolina.
[6] Black Mountain, North Carolina.

TABLE 1

A chronological summary of the literature reporting on the results of the use of pneumoperitoneum (PP) as treatment for pulmonary tuberculosis

AUTHOR	NUMBER OF CASES	PROGNOSIS	MAXIMAL PERIOD OBSERVATION	PRIOR COLLAPSE		GOOD RESULT	REMARKS
				Phrenic	Any		
1937							
Johannides *et al.* (53)	3	Poor	Short	100%	100%	100%	Recommend phrenic plus PP
Trimble *et al.* (83)	80	Poor	1 yr.	Most	100%	Some	A preliminary report
Fremmel (45)	8	?	18 mos.	100%	100%	50%	
1938							
Trimble (84)	250	Poor	Short	?	?	1.6%	Unfavorable
Burge (30)	3	Poor	Short	0	0	?	Recommend PP without phrenic
Hobby (51)	19	?	Short	?	?	Many	Favorable
Daniels *et al.* (37)	21	Poor	1 yr.	100%	100%	72%	8 prepared for surgery
Stokes (80)	41	Poor	2 yrs.	100%	100%	22%	Small doses; PP has limited use
Bennett (24)	200	Poor	2 yrs.	87%	100%	Many	Mid and lower third cavities close more readily than upper third
Choussat (33)	1	?	9 mos.	?	?	100%	PP relieves tuberculous peritonitis
Banyai (11)	120	?	?	?	?	Many	Series of 220 treated for tuberculous enteritis and peritonitis
Mercador *et al.* (63)	3	Poor	Short	?	?	Many	PP relieves digestive symptoms
Gomez *et al.* (46)	Few	Poor	2 yrs.	Most	Many	?	Used mostly for tuberculous peritonitis
1939							
Brian *et al.* (26)	3	Poor	1 yr.	100%	100%	100%	Selected cases; never used PP alone
Bruce (29)	4	Poor	Short	100%	100%	75%	Symptomatic improvement only
Trimble *et al.* (85)	152	Poor	3 yrs.	Most	100%	Few	Unfavorable: 20 autopsies
Mellies (62)	93	Poor	3½ yrs.	Most	Most	66%	22.5% sputum conversion
Centoscudi *et al.* (32)	30	?	4 yrs.	?	?	Many	Effective in selected cases
Barnes (22)	1	—	3 mos.	0	?	?	Given for three months post-partum to let diaphragms down gradually
Hernandez *et al.* (49)	3	Poor	Short	?	?	66%	Favorable
1940							
Banyai (20)	30	?	?	?	?	?	Favorable; no figures
Nunez Bachiller (64)	?	?	2 yrs.	?	?	Many	Right basal lesions least apt to improve with PP

TABLE 1—*Continued*

AUTHOR	NUMBER OF CASES	PROGNOSIS	MAXIMAL PERIOD OBSERVATION	PRIOR COLLAPSE		GOOD RESULT	REMARKS
				Phrenic	Any		
1940—*Cont.*							
Katz (54)	4	?	5 mos.	?	?	100%	Favorable
Boisliniere *et al.* (25)	50	Poor	18 mos.	18%	50%	60%	21 took PP three months or less
Adelman (1)	3	?	2 yrs.	100%	100%	100%	Used mostly for abdominal tuberculosis
Orsi (66)	5	?	1 yr.	?	?	100%	
McIntyre (60)	11	Poor	2 yrs.	Most	Most	45%	Best method for advanced bilateral tuberculosis
Harrell (48)	12	Poor	9 mos.	9%	100%	25%	
1941							
Brian *et al.* (27)	15	Poor	2 yrs.	100%	100%	100%	
Dongrey (39)	38	Poor	2 yrs.	?	Most	Many	Only 3 sputum conversions
Trimble (86)	300	Poor	7 yrs.	?	Most	Many	Opinion changed; PP recommended without phrenic
Fowler (44)	56	Fair	3 yrs.	Some	Most	54%	11% prepared for surgery; hemoptysis controlled in 7 cases
Rilance *et al.* (72)	55	Fair	?	100%	100%	35%	PP is technically difficult
Allen (2)	4	Fair	3 yrs.	50%	100%	Many	
Lefèvre *et al.* (56)	5	?	3½ yrs.	Most	Most	?	Results not made clear
Sanchez Acosta *et al.* (77)	50	?	?	?	?	26%	No cures
Hernandez Diaz (50)	5	?	3 yrs.	Most	Most	?	5 good results; total not clear
1942							
Lopez Sendon *et al.* (58)	26	?	1 yr.	100%	100%	Few	Unfavorable
Woodford (90)	1	Poor	3 yrs.	100%	100%	100%	
Raimondi (70)	?	Poor	4½ yrs.	?	?	?	A few excellent results
Itturiaga (52)	5	?	?	?	?	?	Very good in exudative tuberculosis
1943							
Clifford-Jones *et al.* (34)	60	Poor	2 yrs.	100%	100%	Some	PP used for short periods only
Disney (38)	38	Poor	Short	100%	100%	?	Enteritis made worse by PP
Keers (55)	1	Poor	3 mos.	100%	100%	100%	
Logie (57)	1	Poor	1 mo.	0	0	100%	Controlled severe hemorrhage
Mallick *et al.* (59)	156	?	1 yr.	?	?	50%	Best in exudative tuberculosis
Tempel (82)	7	Poor	3 yrs.	100%	100%	100%	Used with pneumothorax
McShane (61)	4	Poor	4 yrs.	100%	100%	100%	Old pneumothorax space obliterated in one case

TABLE 1—*Concluded*

AUTHOR	NUMBER OF CASES	PROGNOSIS	MAXIMAL PERIOD OBSERVATION	PRIOR COLLAPSE		GOOD RESULT	REMARKS
				Phrenic	Any		
1944							
de los Rios (74)	200	?	?	50%	?	80%	Favorable, but vague
Stuart (81)	1	Fair	3 yrs.	100%	100%	100%	
Drury *et al.* (41)	28	?	Short	76%	?	Most	Used post-partum in a few cases
Rilance *et al.* (73)	101	Fair	4 yrs.	50%	50%	50%	
Crow (35)	223	Fair	5 yrs.	Most	Most	44%	
1945							
Crow *et al.* (36)	546	Fair	5 yrs.	100%	100%	60%	Advises PP as a primary procedure
Anderson *et al.* (3)	110	Fair	4 yrs.	96%	Most	74%	Far advanced: 74% improved or better; moderately advanced: 100% improved or better; 50% sputum conversion; used as a primary procedure altogether
Edwards *et al.* (42)	50	Poor	15 mos.	98%	100%	50%	10% "success"; 40% "improved"
Schmidt (78)	61	Poor	4 yrs.	Most	Most	?	An X-ray discussion only
Proton *et al.* (68)	15	?	Short	Most	?	Many	Favorable

and complications, without specific figures on results or follow-up studies. Even Banyai's new text (21) is deficient in this regard.

After eliminating data on the use of pneumoperitoneum in intestinal and peritoneal tuberculosis, it is apparent that, despite the size of the bibliography, there is all too little concrete evidence on which to weigh the effectiveness of the procedure.

Finally, while over 90 per cent of those writing on the subject apparently consider pneumoperitoneum a definitely useful procedure, that it is not so judged by most tuberculosis physicians is a fact made obvious both by wide-spread personal comment and avoidance of the procedure (40).

TECHNIQUE

The technique of administering artificial pneumoperitoneum has been frequently described. Our method has developed along simple lines and has been so safe in many hands over a ten-year period that it is briefly outlined, together with pertinent data on the continuation of treatment.

All injections are given at a site about 2 inches to the left and below the umbilicus. This area is surgically prepared and infiltrated with 1 per cent procaine. A 1-inch, 25-gauge needle is then deeply inserted and infiltration of the peritoneum is carried out. A puncture wound of the skin is made with a sharp needle. Then, for the initial treatment, a 1½-inch, 19-gauge, short-bevel needle is used, in which a small hole has been drilled 1 to 2 mm. from the tip on the long side; this is attached to a 2 cc. hypodermic syringe and penetration through the skin and at least two layers of resistant tissue (pos-

terior rectus sheath and peritoneum) is made with a firm perpendicular twisting pressure. At this point, the syringe is removed and 2 cc. of air are gently pressed into the needle. If this air returns to the syringe easily on drawing back on the plunger several times, the air has presumably been forced into a confined space outside the peritoneal cavity; if the air injected is lost, one may conclude that he is in contact with the peritoneal cavity, and a 1 to 2 mm. further penetration is very carefully made.

The pneumothorax apparatus is then connected with the needle and air is slowly displaced into the needle. If the patient complains of pain at the site of injection when air is given, it is considered that the opening of the needle is not in the peritoneal cavity and further penetration should be made. Mild aching in the shoulders or anterior chest may be noticed, usually some time after administration of air.

Occasionally these tests are inconclusive. Bearing in mind the possibility of penetration of the gut, as in the presence of adhesive peritonitis with a loop of bowel adherent to the inside of the abdominal wall, a new area a few centimeters away is utilized. Rarely, a longer 3-inch "initial" needle will be needed to penetrate thick-walled abdomens.

While manometric readings, which incidentally are more positive on inspiration and less positive on expiration, are not always obtainable initially, fluctuations obtained may be of some value in determining the presence of the needle in a free peritoneal space.

The initial dose of air varies from 300 cc. to 2,500 cc., depending on the indication: large doses are used to control hemorrhage. The average routine initial dose was 500 cc. and the average second dose was 800 cc.

There is a remarkable variation in the capacity of different abdomens and in tolerance to both the acknowledged early discomfort of pneumoperitoneum and psychogenic factors. This early abdominal and chest pain, aggravated on bending and rolling over in bed, presents a problem not because of its severity, but because, in contradistinction, pneumothorax is relatively painless.

Fluoroscopy in the erect position after the initial dose will usually disclose air under one or both diaphragms and thereby confirm the presence of air in the desired location.

Preoperative medication appears unnecessary except in highly nervous patients. Mild postoperative analgesia may be needed for from two days to two weeks, but can often be avoided by judicious reduction in the amount of air and by technical skill in avoding extraperitoneal administration of air.

The second dose is usually given on the second or third day, the third on the fourth or fifth day, and subsequent doses twice a week, once a week, once in ten days and in some patients, once in two weeks.

The size of refills was also quite variable and ranged from 400 cc. in a small stout person or in one with many peritoneal adhesions, to as much as 3,000 cc. every two weeks in a large multiparous woman with a relaxed abdominal wall. Manometric pressure was seldom carried above plus 8, and often was around plus 5. The average maintenance dose per week in our series of around 40,000 refills was 1,250 cc. in white males, 1,285 cc. in white females, 1,095 cc. in colored males and 1,065 cc. in colored females; or an overall average of 1,165 cc. per week.

As soon as the peritoneal cavity is well distended by refills during three to six weeks or more, the space is entered in one thrust with a plain 1½-inch, 19 gauge, sharp-bevel needle attached to the syringe as before, but without the use of procaine. By this time the administration of pneumoperitoneum is remarkably simple.

Abdominal binders are usually tried after a few weeks of treatment and, if well tolerated, are used continuously. We have recently been able to demonstrate by fluoroscopy in a series of patients that a slight further elevation and slight further limitation of

motion on both quiet and deep respiration of one or both diaphragms may be obtained in many patients with a well-fitted binder. Some seem better able to tolerate pneumoperitoneum wearing the binder, and many are able to space refills out to a longer interval by gradually tightening the binder between them.

A special binder is gradually being evolved for us.[7] Figure 1 shows a patient wearing the most recent model.

Pneumoperitoneum therapy has been continued in much the same manner as pneumothorax or a course of phrenic nerve crushes, that is, until the disease is well under control or its particular purpose has been accomplished. There is reason to believe that

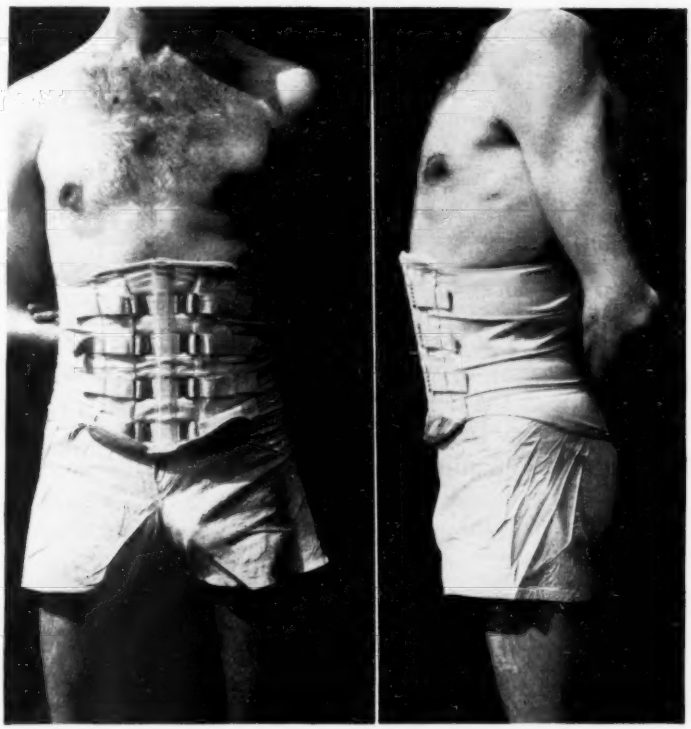


FIG. 1. Special pneumoperitoneum binder.

an effective pneumoperitoneum, when it is not used to prepare the patient for chest surgery, should be continued somewhat longer than pneumothorax (table 5).

Treatment was abandoned for failure to obtain satisfactory diaphragmatic elevation (5 cm. or more), for failure to obtain roentgenological and/or symptomatic benefit, because of certain complications, and, in a few, because of individual unwillingness to tolerate enough air to cause effective diaphragmatic elevation.

[7] Through the courtesy of Spencer, Incorporated, New Haven, Connecticut, to whom we are indebted.

RESULTS

Table 2 shows the principal form of treatment used in all cases of reinfection pulmonary tuberculosis at the North Carolina Sanatorium for ten years. The distribution of treatment at the Eastern North Carolina Sanatorium was roughly parallel. The chart is divided into colored and white patients and starts one year before the first patient taking pneumoperitoneum was discharged from each division. The increasing use of pneumoperitoneum is apparent; at the time of this report, it had reached a peak at 36 per cent of colored and 25.3 per cent of white patients out of an average census of 710 patients with reinfection type pulmonary tuberculosis at both institutions.

In evaluating pneumoperitoneum, cases falling into the following categories were considered "satisfactory" results:

(*a*) All cavities closed by roentgenogram and fluoroscopy, and sputum converted to negative.[8]

(*b*) "Preparation for chest surgery," which covers reduction in size of cavities on the operated side, closure of cavities on the other side and clearing of infiltration on either side (see example in figure 4).

(*c*) "Improved," which includes closure of some but not all cavities, reduction in cavity size, extensive clearing of infiltration, obliteration of an old pneumothorax space, obliteration of a chronic empyema space with or without bronchopleural fistula (figure 6), or definite improvement in symptoms and general condition persisting up to the time of loss of contact or to the date of this report.

No case was classified as "satisfactory" unless the improvement was coincident with a satisfactory diaphragmatic rise after pneumoperitoneum therapy was started. Control of hemoptysis, although "satisfactory," was considered too temporary an effect to evaluate together with factors of a more permanent nature and, therefore, is not included in the figures as a "satisfactory" result.

"Unsatisfactory" results were:

(*a*) "Temporary symptomatic improvement," which includes all those with relief of symptoms and/or roentgenological improvement but with eventual progression of the disease while under pneumoperitoneum treatment.

(*b*) No demonstrable benefit, including the serious complications of pneumoperitoneum.

Table 3 summarizes the clinical data of the 474[9] patients prior to treatment with pneumoperitoneum for three months or longer. It is evident that most of the subjects were poor-risk advanced cases, and that pneumoperitoneum was used principally when pneumothorax was either unsatisfactory or impossible, diaphragmatic paralysis ineffective or inapplicable, or major chest surgery contraindicated or unavailable. Most of the few patients not classified as far advanced were treated in the last two years.

[8] Sputum conversion is based throughout this report on twenty-four, forty-eight and seventy-two hour concentrations varying from 2 to 16 in number, and persisting negative through the ambulant stage before discharge.

[9] 407 at the North Carolina Sanatorium, capacity 600 beds, and 67 at the Eastern North Carolina Sanatorium, capacity 180 beds.

TABLE 2

Distribution of principal forms of therapy for all patients discharged from the North Carolina Sanatorium with reinfection pulmonary tuberculosis from July 1, 1937 to July 1, 1946, plus those resident on July 1, 1946

(Prison Division patients are not included)

YEAR		BED-REST ONLY	PNEUMOTHORAX	PNEUMOTHORAX PLUS PHRENIC	PHRENIC	CHEST SURGERY	PP THREE MONTHS OR MORE	OLEOTHORAX	IN SANATORIUM LESS THAN THREE MONTHS	TOTAL	PP LESS THAN THREE MONTHS
1937–38	W	—	—	—	—	—	—	—	—	—	—
	C	57	22	3	12	2	0	0	37	133	0
	T	—	—	—	—	—	—	—	—	—	—
1938–39	W	—	—	—	—	—	—	—	—	—	—
	C	57	31	9	22	4	2	0	34	159	4
	T	—	—	—	—	—	—	—	—	—	—
1939–40	W	69	78	22	57	11	0	0	35	272	0
	C	61	41	16	11	6	20	9	36	201	6
	T	130	119	38	68	17	20	9	71	473	6
1940–41	W	67	49	45	28	16	5	0	33	243	6
	C	89	64	24	17	7	21	4	56	284	11
	T	156	113	69	45	23	26	4	89	527	17
1941–42	W	83	65	30	40	15	7	0	37	277	4
	C	90	32	44	12	4	17	1	44	244	9
	T	173	97	74	62	19	24	1	81	521	13
1942–43	W	80	44	15	39	12	5	0	43	238	5
	C	82	32	25	31	8	22	0	38	248	12
	T	162	76	40	70	20	27	0	81	486	17
1943–44	W	72	39	25	32	15	11	0	37	231	8
	C	62	39	31	33	5	15	1	35	221	6
	T	134	78	56	65	20	26	1	72	452	14
1944–45	W	54	36	25	39	13	7	0	42	216	7
	C	63	40	20	40	10	16	0	37	226	15
	T	117	76	45	79	23	23	0	79	442	22
1945–46	W	44	47	28	55	18	54	0	74	320	20
	C	77	27	12	27	4	39	0	68	254	39
	T	121	74	40	82	22	92	0	142	574	59
Resident patients July 1, 1946	W	56	36	27	25	44	63	0	15	266	32
	C	70	34	15	24	11	71	0	15	222	24
	T	126	70	42	49	55	134	0	30	488	56
Totals	W						165				82
	C						242				126
	T						407				208

W: white—C: colored—T: total

Note: The first discharge of a patient who had taken pneumoperitoneum was 4–11–39 at the Colored Division, and 7–28–40 at the White Division.

Table 4 subdivides the results of therapy into "satisfactory" and "unsatisfactory," and differentiates the white and colored patients in whom pneumo-

TABLE 3

Summary of pertinent data in 474 cases prior to pneumoperitoneum therapy

	WHITE DIVISION	COLORED DIVISION	TOTAL
Number of cases	188	286	474
Sex:			
Male	44%	47%	46%
Female	56%	53%	54%
Age:			
Range	14–69	8–67	8–69
Average	35.4	28.2	31.2
NTA classification before treatment:			
Far advanced	84%	91%	89%
Moderately advanced	16%	9%	11%
Minimal	0	0	0
Prognosis:			
Good	1%	0.5%	0.4%
Fair	24%	15%	18%
Poor	62%	66%	65%
Desperate	13%	18.5%	16.6%
Sputum positive	99%	100%	99.7%
Cavitation:			
Any	99.5%	99.2%	99.3%
Multiple	Most	Most	Most
Bilateral (approx.)	50%	75%	65%
Bilateral disease	100%	100%	100%
Pneumothorax failure before PP	74%	74%	74%
Diaphragmatic paralysis three months or more before PP	62%	52%	56%
Pneumothorax and/or diaphragmatic paralysis before PP	99%	82%	88%*

* The 12 per cent who had no prior collapse therapy fall almost entirely within the group discharged 1945–46 and the resident patients.

peritoneum was used alone, in combination with a paralyzed diaphragm (figure 3), and in combination with pneumothorax with or without diaphragmatic paralysis.

On the white service the results were consistent and roughly the same whether pneumoperitoneum was combined with other collapse measures or not, the average being 57 per cent "satisfactory."

TABLE 4

Results of pneumoperitoneum therapy at the North Carolina Sanatorium 1937–46, and Eastern North Carolina Sanatorium 1943–46, used alone and in combination with diaphragmatic paralysis and pneumothorax, subdivided into white (W) and colored (C) patients

	WITH DIAPHRAGMATIC PARALYSIS				ALONE: WITHOUT PARALYSIS OF EITHER DIAPHRAGM**		WITH PNEUMOTHORAX		TOTAL	
	With a definitely paralyzed diaphragm		With a possibly paralyzed diaphragm*							
	W	C	W	C	W	C	W	C	W	C
Total treated	96	130	7	22	69	128	16	6	188	286
(both W and C)	226		29		197		22		474	
Satisfactory results										
Cavities closed; sputum negative	15	13	2	1	15	14	3	1	35	29
Prepared for chest surgery	24	22	0	3	9	6	2	1	35	32
Definitely improved	19	22	3	2	12	18	4	2	38	44
Total number	58	57	5	6	36	38	9	4	108	105
(both W and C)	115		11		74		13		213	
Total per cent	60	44	71	27	52	30	56	67	57	37
(both W and C)	51		38		37		59		45	
Unsatisfactory results										
Temporary symptomatic improvement	15	17	1	6	7	23	3	0	26	46
No improvement or worse	23	56	1	10	26	67	4	2	54	135
Total number	38	73	2	16	33	90	7	2	80	181
(both W and C)	111		18		123		9		261	
Total per cent	40	56	29	73	48	70	44	33	43	63
(both W and C)	49		62		63		41		55	

* A phrenic operation had been done prior to pneumoperitoneum, but either the status of diaphragmatic paralysis at this time was not clearly stated in the record, or there had been only a partial resumption of function of a previously paralyzed diaphragm.

** A number of these cases had had previous diaphragmatic paralyses, but function had been regained prior to or about coincident with the institution of pneumoperitoneum therapy.

On the colored service results were definitely poorer, being 37 per cent "satisfactory" of the total, and less consistent in that pneumoperitoneum alone was less effective than when combined with diaphragmatic paralysis.

It should be pointed out that no attempt was made to evaluate the relative effect of diaphragmatic paralysis and pneumoperitoneum when both were used; if pneumoperitoneum was used for more than three months, the case was included in this series. The series was not controlled by a preliminary period of

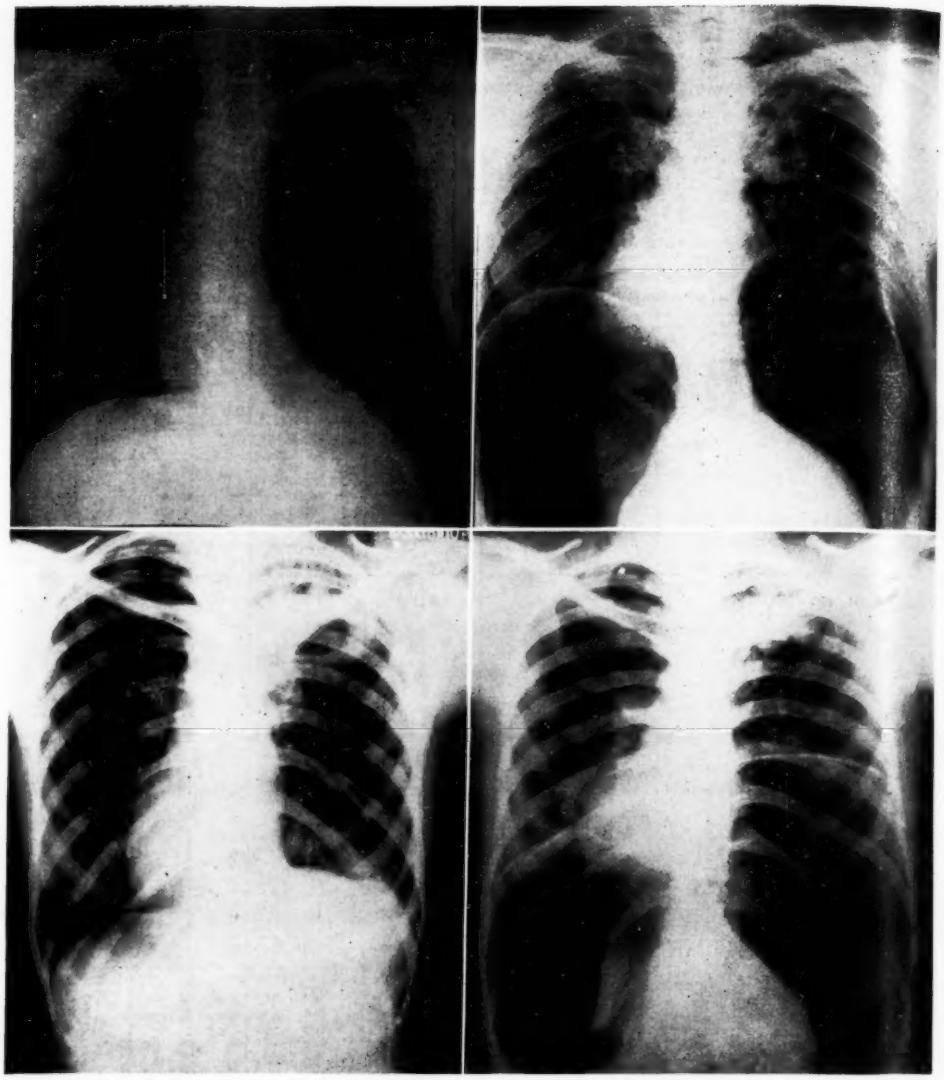


FIG. 2a. (Upper left.) *Pneumoperitoneum alone:* Film date 12–31–45 on J. O., a 27-year-old white male, admitted 12–28–45 with far advanced, B, disease with extensive bilateral involvement and multiple small cavities. Sputum positive on direct smear. Extensive spread had occurred during previous six months.

FIG. 2b. (Upper right.) Film dated 9–28–46 on J. O. shows much clearing and cavity closure from pneumoperitoneum which was instituted 1–12–46; 7 negative seventy-two-hour concentrations since 5–15–46; progressively ambulant since 6–20–46.

FIG. 3a. (Lower left.) *Pneumoperitoneum plus diaphragmatic paralysis:* Film dated 5–12–41 on H. J., a 23-year-old colored female, admitted 5–11–41 with far advanced, C, disease, consisting chiefly in a large cavity in the right upper lobe. Sputum positive on direct smear. Right pneumothorax failed 5–15–41. Pneumoperitoneum was begun 5–22–41; phrenic crush was added on right 6–5–41. Cavity closed and sputum converted to negative in October, 1941.

FIG. 3b. (Lower right.) Film dated 1–23–43 on H. J. shows cavity now closed. Discharged home 2–7–43 after 15 negative sputa. In July, 1946 she was doing house work full-time, feeling well, still taking pneumoperitoneum, lesion stable by roentgenogram and 2 twenty-four-hour concentrations were negative.

bed-rest in most cases, nor by a parallel series on bed-rest. However, all cases in which there was real doubt of there being a "satisfactory" outcome were placed in one of the two "unsatisfactory" categories.

Included among the "improved" patients are 3 instances of successful obliteration of old pneumothorax spaces in which the lung had failed to reëxpand after prolonged observation on bed-rest; also included are 5 cases of obliteration of still infected empyema spaces, 2 of which were complicated by bronchopleural fistulae. The use of pneumoperitoneum for this purpose was first reported by Mellies in 1939 (62).

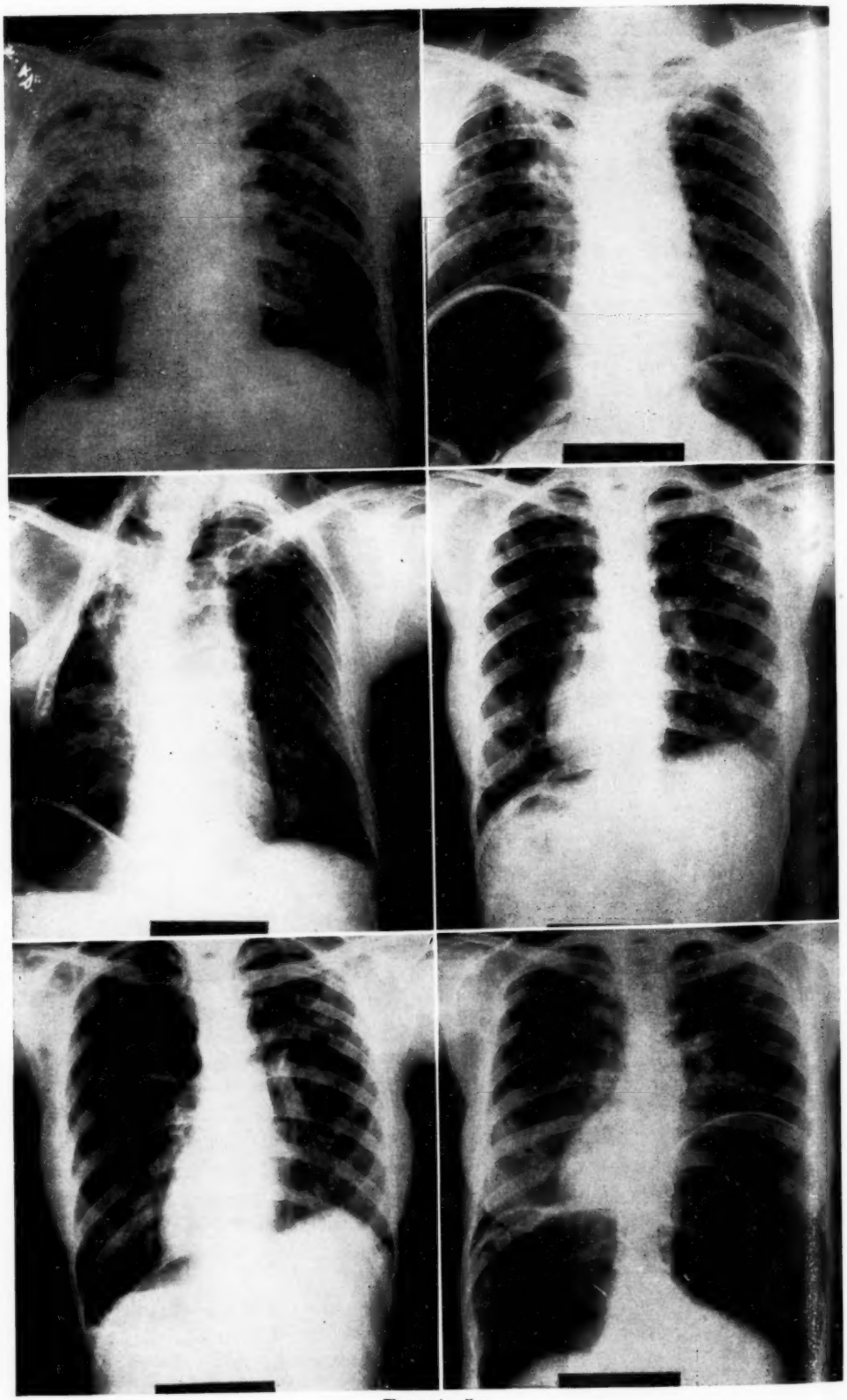
Attention is also called to the 26 white and 46 colored patients who showed temporary symptomatic improvement. Although many of these patients ultimately died or were sent home or to another institution as unimproved, their relief from cough, ease in raising sputum, lowered temperature and feeling of well-being were gratifying, at least for a time. Some so classified were improved roentgenologically and/or clinically for many months only to suffer a relapse. In addition, many of the 236 patients who took pneumoperitoneum for less than three months were afforded symptomatic relief and, at times, control of hemoptysis in their last days, and nearby patients were often spared from listening to severe and prolonged coughing.

The average duration of treatment in the sanatorium among those who took pneumoperitoneum for three months or longer was 51.8 weeks; 54.5 weeks in white patients, and 50.5 weeks in colored.

Pneumoperitoneum is known to have been continued after discharge in 156 patients. Follow-up studies revealed that 42 have now received treatment over two years, 14 over three years, 8 over four years and 4 over five years.

The duration of sanatorium plus post-sanatorium pneumoperitoneum treatment of "satisfactory" cases with cavity closure and sputum conversion, not requiring eventual chest surgery, has lasted up to almost six years. Follow-up of all 41 such patients yielded the following information: 21 were alive and apparently well, many working, with cavities still closed according to recent roentgenograms and sputum negative on at least one recent test (routine smear or twenty-four-hour concentration; no gastric specimens, cultures or animal inoculations were used), observed over periods of from four months to four and one-half years following discharge, or an average of eighteen months; 95 per cent took pneumoperitoneum after discharge for an average of eighteen months. In addition to these 21, 3 now require chest surgery after one, three and one-half and four and one-half years, respectively; 2 have reactivated tuberculosis after one and three years; 2 are dead, three and five years after discharge, cause undetermined; one died following a "stroke" two years after discharge; one died of tuberculosis five years after discharge and three years after stopping pneumoperitoneum in good general condition; one died of tuberculosis four years after discharge despite resumption of pneumoperitoneum. No information is available on 10.

So far only 14 such "satisfactory" cases have discontinued treatment (see table 5). The duration of treatment in these cases varied from 49 to 247 weeks, an average of 133 weeks. Only 8 have been observed over one year after stop-



FIGS. 4a–5c

ping pneumoperitoneum, too few from which to attempt to derive any statistical data.

The duration of treatment in preparation for chest surgery when "satisfactory" results were obtained was from 18 to 239 weeks or an average of 79.4 weeks. Follow-up on all 66 patients classified as "prepared for chest surgery" yielded the following results: 23 were doing well and sputum-negative one month to four years, average twenty months, after surgery; one is now doing well one year after revision of a two-stage thoracoplasty; 13 were still sputum-positive but apparently improved two to fourteen months after surgery; 5 died during or soon after surgery (10 per cent operative mortality); 2 are now respiratory cripples following surgery; 2 had reactivation of disease one and three and one-half years after surgery; no information is available on 3 after successful completion of surgery; one was murdered at home while awaiting surgery; 16 are still awaiting surgery in the hospital.

Eleven of these surgical patients received extrapleural pneumonolysis with packing of methyl methacrylate (lucite) spheres, an ingenious and apparently successful revival of an old approach to the collapse problem by Wilson and Baker (89). One death occurred in this group.

COMPLICATIONS

The following complications of pneumoperitoneum, used to treat pulmonary tuberculosis, have been reported in the literature. Most articles report serous

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FIG. 4a. (Upper left.) *Pneumoperitoneum in preparation for chest surgery:* Film dated 4-21-41 on E. W., a 41-year-old white male, admitted 4-20-41 with far advanced, C, disease; there is heavy caseation and some cavitation on the left, plus heavy active involvement on the right. Sputum positive on direct smear. Left pneumothorax was abandoned 4-28-41 after a "spontaneous" pneumothorax. Left phrenic crush 6-10-41.

FIG. 4b. (Upper right.) Film dated 8-8-44 on E. W. shows much clearing on both sides after pneumoperitoneum was started 4-19-43, but sputum still positive and left apical cavity still open.

FIG. 4c. (Centre left.) Film dated 3-21-46 on E. W. taken just prior to discharge from sanatorium shows end-result of eight-rib two-stage thoracoplasty completed 2-29-45. Pneumoperitoneum was abandoned 1-22-45 just prior to operation. Eight negative sputum concentrations since 3-13-45. In July, 1946 he was working four hours per day, 2 sputum concentrations were negative, he was feeling well and lesions were stable by routine postero-anterior and Bucky roentgenograms.

FIG. 5a. (Centre right.) *Pneumoperitoneum plus pneumothorax:* Film dated 3-30-42 on M. K., a 28-year-old white female, readmitted 3-24-42 with far advanced, C, disease with bilateral extensive involvement and sputum positive on direct smear. She had had a right phrenic crush 12-27-39; diaphragmatic function had never been fully regained.

FIG. 5b. (Lower left.) Film dated 5-10-43 on M. K. shows satisfactory left pneumothorax which had been instituted 4-6-42, but disease is now worse on right. Sputum still positive on direct smear. Right pneumothorax failed 5-2-43.

FIG. 5c. (Lower right.) Film dated 1-23-44 on M. K. shows effect of pneumoperitoneum which was started 5-14-43; sputum converted 7-7-43 with great relief of cough and expectoration; discharged to part-time duty as nurse in sanatorium 3-1-45; left pneumothorax stopped January, 1946; pneumoperitoneum stopped 6-10-46 because of febrile reactions after refills. Sputum had been persistently negative on many concentrations; then became positive on 2 occasions without change in stable appearance of roentgenograms and without untoward symptoms. Sputum now negative after modified bed-rest for one month.

peritoneal effusions and peritonitis, aggravation of various types of abdominal hernias, subcutaneous emphysema in various locations, dyspnea and abdominal pain. A number of observers have reported puncturing the gut but there are no reports of serious consequences of this accident. Other less common complications reported are: obliterative adhesive peritonitis (3, 26, 83), acute appendicitis occurring eleven times more frequently than the natural expectancy (73), mediastinal emphysema (16), accidental pneumothorax (16, 72), aggrava-

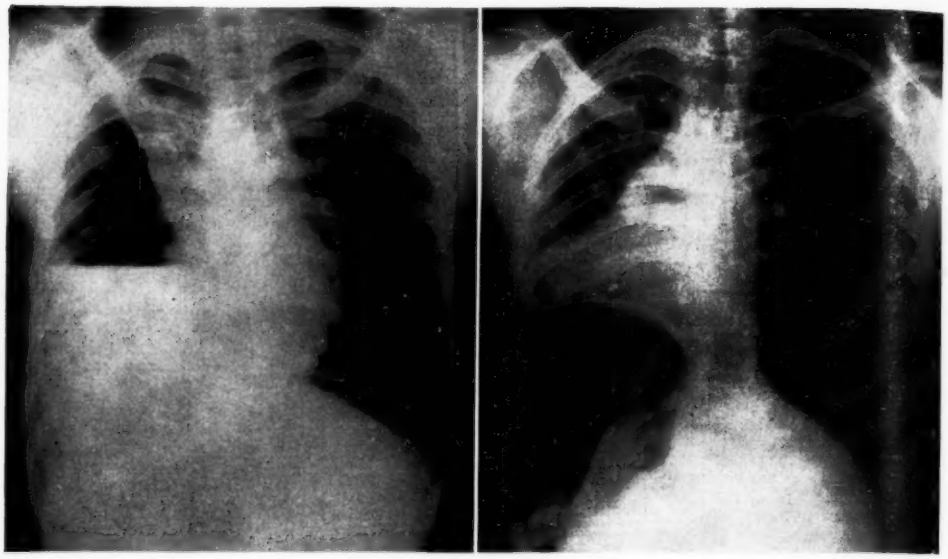

FIG. 6a. (Left.) *Obliteration of empyema space with pneumoperitoneum:* Film dated 3–14–45 on J. C., a 19-year-old colored male, admitted 9–16–44 with far advanced, C, disease, with large cavity in left upper lobe and multiple small cavities in right upper lobe; sputum positive on direct smear. Left pneumothorax was started 11–15–44 and left phrenic crush added 1–9–45; collapse still unsatisfactory and fluid appeared. Pure tuberculous empyema became apparent in late January, 1946; condition failed to improve on repeated aspirations of thick pus and irrigations for six and one-half months.

FIG. 6b. (Right.) Film dated 5–30–46 on J. C. shows reëxpansion of left lung and obliteration of empyema space after pneumoperitoneum was started 8–12–45. The fluid was dried up within three weeks after pneumoperitoneum was started. Right upper lobe cavities no longer visible; now awaiting a left thoracoplasty.

tion of preëxisting heart disease (44), hemoptysis made worse (62), rupture of diaphragm (3), atrophy of diaphragm (62), dysmenorrhea (42, 62), aggravation of preëxisting enteritis (38, 80), hemorrhage from rectum (42), "peritoneal shock" (39), massive atelectasis (26), and lobular atelectasis (62).

Five deaths due to pneumoperitoneum have been reported, 4 due to air embolism (72, 83, 88), and one of sudden death, cause undetermined (48), probably air embolism.[10]

[10] Two more cases of fatal air embolism have been reported, one by G. Roche and J. Giron, Rev. de la tuberc., 1944–45, *9*, 109, and the other by F. A. H. Simmonds, Lancet, April 13, 1946, *250*, 530. [Editor]

† Sputa are twenty-four to seventy-two-hour concentrations.
* Number of sputa not known in these.

TABLE 5

Follow-up of all patients discharged with "satisfactory" results with pneumoperitoneum not supplemented by chest surgery who are known to have abandoned pneumoperitoneum, with or without permission

CASE NUMBER	INITIALS	RACE	AGE	SEX	CLASSIFICATION BEFORE PP	WITH PNEUMOTHORAX	DURATION OF PP IN WEEKS	WEEKS SINCE STOPPING PP	CONDITION DETERMINED MAY–AUGUST, 1946					REMARKS
									X-ray		Recent sputa†	Symptoms	Alive or dead	
									Stable	Unstable cavity				
1	S. G.	C	28	f	FAC	No	106	56	+		Negative*	0	A	Doing full-time housework
2.	L. H.	W	30	f	FAC	No	85	?	Not known				D	PP stopped because of "stroke"
3.	M. L.	C	28	f	FAC	No	212	48	+		Negative*	0	?	Well until March, 1944; no later information
4.	A. R.	C	22	f	FAC	No	91	234		+	Positive	+++	D	Died of pulmonary tuberculosis 10–10–45; had remained asymptomatic over two years after abandoning PP
5.	S. H.	C	30	f	FAB	No	143	164	Not known				D	Sudden death three years after abandoning PP, cause undetermined
6.	M. H.	C	13	m	MAC	No	101	118	+		Negative*	0	A	Working six hours per day
7.	O. O.	C	28	f	FAC	No	174	44	+		2 negative	+	A	Recent loss of 30 lbs.; otherwise well and working; no change by X-ray
8.	N. J.	W	27	f	MAB	No	122	144	+		6 negative	0	A	Working and well
9.	G. L.	W	37	f	FAC	No	178	63	Not known				D	Cause of death undetermined
10.	C. H.	W	43	m	FAC	No	126	84	+		Negative*	0	A	Working and well
11.	M. K.	W	26	f	FAC	Yes	167	4	+		2 positive	0	A	Working part-time for two years; 2 positive sputa four weeks after abandoning PP; now negative
12.	W. B.	W	58	m	MAB	No	49	54	+		None	0	A	Working and well
13.	E. V.	W	32	m	FAB	No	53	18	+		3 negative	0	A	Working four hours per day
14.	T. D.	W	37	m	FAD	Yes	247	8	+		8 negative	0	A	Working four hours per day; still takes right pneumothorax
Averages							133	80						

† Sputa are twenty-four to seventy-two-hour concentrations.
* Number of sputa not known in these.

In our 710 cases there was one death directly traceable to pneumoperitoneum, from air embolism following accidental administration of air into the substance of the liver, unquestionably a breach of technique. There were 2 autopsied cases of mixed infection peritonitis, one of which showed a perforated tuberculous ulcer of the ileum, and in neither was there gross postmortem evidence of a puncture wound of the gut.

The complications observed in this series are listed in table 6. In less than 5 per cent did complications lead to abandonment of pneumoperitoneum. None of the "minor" complications were cause for abandonment, except the febrile reactions following refills. These reactions appeared many months after treatment was started and remain unexplained.

Pneumoperitoneum was abandond because of pain in 46, and dyspnea in 13 patients, two factors not deemed to be true complications. In each instance when pain was the cause of abandonment, it occurred during the first few weeks of therapy.

Unfortunately our records do not show the frequency of intraperitoneal adhesions, but they were observed in varying degree in many cases. Anderson and Winn (3) found them in 71 per cent of patients. In only 5 known cases was it necessary for us to abandon treatment because of such adhesions, usually when the liver and right diaphragm were densely adherent. In one patient, numerous adhesions beneath both diaphragms were severed at laparotomy with subsequent satisfactory diaphragmatic elevation, In one other patient, severance of adhesions was followed by severe shock, apparently due to sudden decompression of the thoracic and abdominal viscera; the patient survived, however, and pneumoperitoneum was continued uneventfully with materially improved diaphragmatic elevation.

Only 3 patients with hernia were unable to continue treatment after applying a well fitted truss.

Needle perforation of the gut during administration of air was suspected clinically on a few occasions, without any serious sequelae.

In one patient a needle, broken during the administration of air, was lost, necessitating a laparotomy to remove it. The patient recovered uneventfully; pneumoperitoneum was not resumed as she came to thoracoplasty a few weeks later.

Peritoneal effusion, clear or cloudy, was observed in a total of 52 patients, or an incidence of 7.3 per cent. Other observers have found the incidence to be 3.8 per cent (44), 8 per cent (36), and 12 per cent (35). Ophuls (65) found that 12 per cent of patients dying of tuberculosis show peritoneal fluid of some degree at autopsy, in the absence of pneumoperitoneum.

Repeated hemoptyses were relieved after removal of pneumoperitoneum in 7 patients.

Acute pleurisy with effusion occurred in 5. The relation, if any, of pleurisy to pneumoperitoneum is not clear, but this incidence seems no more than the natural expectation.

Contrary to the early literature on the subject, improvement in the symptoms

of tuberculous enteritis was not observed in this series. In fact, the patients with severe enteritis usually did poorly on pneumoperitoneum from the standpoint of their pulmonary disease. Since considerably less air was used in treating enteritis and peritonitis with pneumoperitoneum (5), the degree of visceral

TABLE 6

Complications observed in 710 patients receiving pneumoperitoneum

	NUMBER OF CASES	
	Colored	White
Major complications requiring abandonment of pneumoperitoneum in each case		
Serofibrinous peritonitis, tuberculous	12	10
Mixed infection peritonitis	1	1
Massive ascites	2	2
Air embolism, following accidental administration of air into the substance of the liver: immediate death	1	0
Incarcerated femoral hernia (pneumoperitoneum resumed later)	1	0
Spontaneous pneumothorax	1	1
Sudden attacks of abdominal pain following refills, possibly due to air embolism	0	1
Wheezing cough, relieved after pneumoperitoneum was abandoned	0	1
Totals	18	16
Frequency of major complications: 4.7 per cent		
Minor complications		
Clear peritoneal transudate, negative on direct smear and culture for acid-fast organisms (therapy not abandoned)	13	11
Aggravation of hernia:		
inguinal	9	2
umbilical	7	0
postoperative	0	2
Febrile reactions following each refill	1	3
Acute appendicitis	0	1
Hemoptysis, made less severe or relieved by abandoning pneumoperitoneum	6	1
Pleurisy with effusion	0	5
Totals	36	25
Frequency of minor complications: 8.6 per cent		

compression usually accompanying effectively elevated diaphragms may account for this discrepancy. Clinical enteritis may therefore be considered a contraindication.

Table 7 briefly outlines the pertinent abdominal findings in the 17 autopsies obtained on patients who had received pneumoperitoneum.

Diaphragmatic paralysis following phrenic crush may have a greater tendency

to fail to regain normal function in the presence of supplementary pneumoperitoneum. Out of the 474 patients taking pneumoperitoneum longer than three months, there were 193 with sufficient elapsed time after operation and sufficient data in the record to survey. Of these, 42 per cent showed complete and 9.5 per cent partial failure to regain normal function in from one to four years after their phrenic crush. Paralysis was considered complete with a 4 or 5 cm.

TABLE 7

Pertinent abdominal findings in all 17 autopsies performed on patients taking pneumoperitoneum: all showed advanced active pulmonary tuberculosis

INITIALS	COLOR	PERTINENT ABDOMINAL FINDINGS	DURATION OF PNEUMOPERITONEUM TREATMENT IN WEEKS
M. D.	C	Tuberculous adhesive peritonitis with fluid	1
W. R.	W	No pertinent abdominal findings	2
H. H.	W	Severe enteritis; small amount of clear fluid	4
L. S.	C	No pertinent abdominal findings	7
M. D.	W	Severe mixed infection peritonitis; severe enteritis with a perforated ulcer of ileum	14
G. D.	C	No pertinent abdominal findings	18
W. M.	C	Severe tuberculous peritonitis and enteritis	22
W. J.	W	Massive ascites; severe enteritis; caseous mesenteric adenitis; severe portal cirrhosis; (chronic cor pulmonale)	23
G. C.	C	No pertinent abdominal findings	24
R. B.	W	No pertinent abdominal findings	25
G. G.	C	Mild adhesive peritonitis; no fluid	26
C. G.	W	No pertinent abdominal findings	27
J. D.	W	Small amount clear fluid; chronic passive congestion of liver (chronic cor pulmonale, slight); post-surgical death; no abdominal fluid present when pneumoperitoneum was abandoned three months before	28
L. S.	C	Severe enteritis with perforation of an ulcer of ileum and severe tuberculous peritonitis	33
C. M.	C	Severe mixed infection peritonitis	39
M. P.	C	No pertinent abdominal findings	56
J. W.	W	Severe adhesive tuberculous peritonitis with multiple pockets of cloudy fluid; no enteritis	13

elevation and loss of motion or paradoxical motion of the diaphragm. Paralysis was deemed partial in the presence of elevation plus material reduction in descent of the diaphragm on deep inspiration. No allowance was made for age, nor for the factor of adhesions, but all were initial crushes using a uniform technique of three clamps on the main trunk and severance of all accessory branches found.

In a parallel series of 192 initial phrenic crushes, alone and with pneumothorax but without coincident pneumoperitoneum, performed by the same surgeons and controlled in the same manner, 21.3 per cent showed complete and 16.1 per cent partial failure to regain normal function in from one to four years following

the crush. Although the proof is not as yet available, it is believed that excessive stretching and resultant muscular atrophy, plus supra- and subdiaphragmatic adhesions formed during elevation, both play a part in these findings.

The literature on diaphragmatic paralysis yields almost no specific information on permanent loss of function following phrenic crush. Pinner (67) estimates that at least 10 per cent of supposedly temporary diaphragmatic paralyses become permanent and found the literature uninformative. Crow and Whelchel (36) observed only 5 per cent permanent paralyses in their 546 patients taking both pneumoperitoneum and phrenic crush; they recommend dissection of the nerve from its sheath and crushing of the nerve only.

COMMENT

These statistical data are not presented as final proof of the efficacy and safety of pneumoperitoneum. It has been frequently, and correctly, stressed that statistics of tuberculosis treatment are profoundly influenced by the convictions of the author, the lack of controls and the pronounced natural tendency of many cases of tuberculosis to improve spontaneously or on bed-rest alone (67). For instance, since pneumoperitoneum may cause discomfort on bending at the waist, the patient is more apt to stay in bed, a fact which one author thought was the principal advantage of pneumoperitoneum (84). The results, however, seem to have been significantly better than those observed on similar advanced cases on bed-rest alone, before the advent of modern pneumothorax and thoracoplasty.

It also may be fallacious to attempt to distinguish between the effects of pneumoperitoneum alone, and in combination with diaphragmatic paralysis, since experience has demonstrated to our satisfaction that each method has its own indications.

Pneumoperitoneum, both with and without diaphragmatic paralysis, provides a simple reversible method of reducing lung volume, uni- or bilaterally, to a variable degree. The amount of useful pulmonary relaxation obtainable therewith is unpredictable in the individual case until it has been tried.

It is believed that pneumothorax and primary thoracoplasty should always be considered, and even that pneumothorax should usually be attempted where indicated, before pneumoperitoneum is applied.

However, pneumoperitoneum alone now seems preferable to conventional collapse therapy or simple bed-rest in the case with fairly extensive, bilateral, predominantly productive disease with positive sputum, provided the cavities are not too old or thick-walled (figure 2).

Pneumoperitoneum plus diaphragmatic paralysis is useful in those patients in whom one can be fairly certain of the side from which positive sputum is coming. When the source of positive sputum is not clear after thorough study, pneumoperitoneum alone is recommended for a trial period of from two to six months, since supplementary diaphragmatic paralysis often limits the compression effect of pneumoperitoneum to that side.

Another advantage of applying pneumoperitoneum before diaphragmatic

paralysis is the information gained therewith regarding the mobility and attainable elevation of the diaphragm to be paralyzed (36).

It has been emphasized that pneumoperitoneum may convert an ineffective diaphragmatic paralysis into an effective elevated one. It is believed that pneumoperitoneum may further improve upon diaphragmatic paralysis with a good rise, by abolishing the paradoxical motion thereof (62),which theoretically impairs pulmonary drainage (67).

Pneumoperitoneum has the tremendous advantage over pneumothorax of greater safety and freedom from a variety of serious early and late complications. It has a most practical advantage over pneumothorax and all major forms of surgical collapse in the ease of following the effects of treatment by roentgenograms (36). With almost no exceptions, it may be abandoned and reëstablished at will, the space never having been lost to an adhesive peritonitis in our experience.

An "effective pneumothorax" (69) is still unquestionably the most satisfactory collapse measure for pulmonary tuberculosis; but, that it is very limited in its practical application in all those needing collapse therapy cannot be denied. A phrenic crush with good diaphragmatic elevation appears to be amazingly effective at times, in selected cases. Thoracoplasty is now a safe and most dependable procedure in increasing numbers of cases, when they are properly selected and prepared.

However, the vast problem of advanced, particularly bilateral, tuberculosis as seen so frequently in state and county sanatoria remains largely unsolved by these accepted measures.

It is contended that pneumoperitoneum has an important place in the treatment of many of these advanced cases, particularly those with bilateral cavitation, in which pneumothorax is contraindicated, fails or must be abandoned, and major surgery impossible. The practical consideration of the continuing relative unavailability of thoracoplasty in some localities, because of the shortage of facilities, trained personnel and funds must not be overlooked.

CONCLUSIONS

1. In producing a temporary reversible reduction in lung volume, pneumoperitoneum provides an effective measure for the treatment of many cases of advanced pulmonary tuberculosis.

2. Pneumoperitoneum will help prepare many advanced bilateral cases for major chest surgery.

3. In direct contrast to pneumothorax, pneumoperitoneum is a simple safe procedure with only rare serious complications and sequelae, when correctly used.

4. The possibility of using pneumoperitoneum should always be considered in planning the treatment of advanced pulmonary tuberculosis.

SUMMARY

1. The existing literature on pneumoperitoneum is lacking in detailed reports on results of treatment followed over prolonged periods.

2. While the vast majority of the literature is favorable, pneumoperitoneum remains in relative disrepute in most quarters.

3. Our observations indicate that pneumoperitoneum is an easy, safe procedure and requires less judgment and experience to apply than pneumothorax.

4. The use of pneumoperitoneum for an average of 54.5 weeks was responsible for 57 per cent satisfactory results in 188 white patients and, used for an average of 50.5 weeks, was responsible for 37 per cent satisfactory results in 286 colored patients with advanced pulmonary tuberculosis, not amenable to conventional forms of collapse therapy.

5. Pneumoperitoneum was useful in relieving symptoms in terminal pulmonary tuberculosis.

6. Pneumoperitoneum was occasionally useful in helping reëxpand an "unexpandable" lung and in obliterating empyema space, and in controlling pulmonary hemorrhage, when other methods failed.

7. An abdominal binder is a useful adjunct to pneumoperitoneum in most patients.

8. The complications of pneumoperitoneum given to 710 patients for periods ranging from one dose to 306 weeks were minor in 8.6 per cent, and "major" in 4.7 per cent; pneumoperitoneum was the direct cause of death in one case.

9. Pneumoperitoneum was responsible for a significant increase in the failure of diaphragms to regain normal function following phrenic crush.

10. The presence of tuberculous enteritis was associated with frequent failure of pulmonary tuberculosis to show a satisfactory response to pneumoperitoneum in amounts large enough to cause effective diaphragmatic elevation.

SUMARIO

1. En la literatura relativa al neumoperitoneo no figuran informes pormenorizados acerca de los resultados terapeúticos observados durante períodos prolongados.

2. Aunque la inmensa mayoría de la literatura se muestra favorable, el neumoperitoneo continúa en general en descrédito relativo.

3. Las observaciones de los autores indican que el neumoperitoneo es un procedimiento sencillo e inocuo cuya aplicación exige menos juicio y experiencia que el neumotórax.

4. El empleo del neumoperitoneo durante un período de 54.5 semanas obtuvo 75% de resultados satisfactorios en 188 enfermos blancos, y utilizado durante un promedio de 50.5 semanas, obtuvo 37% de resultados satisfactorios en 286 enfermos de color con tuberculosis pulmonar avanzada que no cedía a las formas habituales de la colapsoterapia.

5. El neumoperitoneo resultó útil para aliviar los síntomas en la tuberculosis pulmonar terminal.

6. El neumoperitoneo resultó, de cuando en cuando, útil para ayudar a reexpandir un pulmón "inexpandible" y para obliterar el espacio empiemático y cohibir la hemorragia pulmonar cuando fracasaban otros métodos.

7. En la mayor parte de los enfermos una faja abdominal resultó un coadyuvante útil del neumoperitoneo.

8. Las complicaciones del neumoperitoneo administrado a 710 enfermos durante períodos que variaron de una dosis a 306 semanas, fueron de menor importancia en 8.6% y de "mayor importancia" en 4.7% siendo la causa directa de la muerte en un caso.

9. El neumoperitoneo fué la causa de un aumento significativo de la capacidad de los diafragmas para recuperar su función normal consecutivamente a la trituración del frénico.

10. La enteritis tuberculosa fué aparentemente una contraindicación del empleo del neumoperitoneo a dosis suficientes para el tratamiento eficaz de la tuberculosis pulmonar.

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TRANSVERSE MYELITIS ACCOMPANYING TUBERCULOUS MENINGITIS[1,2]

R. H. RIGDON

Tuberculous infection of the brain, spinal cord and their coverings is a common pathological process. The clinical manifestations in such cases indicate frequent involvement of the brain and its meninges when compared to that of the spinal cord and its meninges. This variation may be explained by the difference in quantity of tissue rather than by either specific affinity of the tissue for this bacterium and its toxin, or on any anatomical bases.

Tuberculous involvement of the spinal cord in this instance may be considered to be either a metastatic lesion or the result of a direction extension of the infection from adjacent tissues. Toxins from this organism at one time were considered to be significant in the production of necrosis of the spinal cord (1). Rich (2) in discussing tuberculous meningitis says, "the entire appearance is that of a severe hypersensitive reaction, with marked inflammation and necrosis. The infection not infrequently extends along the blood vessels into the superficial layer of the cortex. In addition, small superficial infarctions of the cortex may result from occlusion of infected vessels. The symptoms of tuberculous meningitis appear to be due principally to five effects upon the central nervous system: (*1*) Mechanical irritation, (*2*) hypersensitivity, (*3*) vascular obstruction, (*4*) extension of infection to the nervous system, (*5*) increased intracranial pressure."

Solitary tubercles may occur in the spinal cord with or without meningitis. Kupka and Olsen (3) found 87 cases reported in the literature and added one. When a tuberculoma is accompanied by meningitis the clinical manifestations may be both that of a tumor and that of an infection.

The mechanism of the effects produced by Pott's disease on the spinal cord is not obvious in all cases. The cord may be traumatized directly by the collapse of a disintegrating vertebra. An extradural or subdural abscess may be associated with the diseased vertebra and exert pressure on the cord. Cadwalader (4), in an article on paralysis in Pott's disease, reviewed the earlier literature and discussed the problem both from a clinical and pathological standpoint. He said, "I have been able to find only two cases described in which paralysis developed instantaneously without deformity of the vertebrae." In reviewing this problem, Cadwalader cites Kraske who observed pressure on the cord in 6 of 58 cases of Pott's disease. Fischler (5) in 20 cases found compression of the cord produced by a dislocated vertebra in 9 per cent of the cases, by an abscess in 17 per cent, while *pachymeningitis externa* was responsible for 74 per cent of the

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cases. Cadwalader emphasized in his cases of Pott's disease that necrosis of the spinal cord may result from the vascular obstruction that may accompany a tuberculous reaction.

Harbitz (1) observed a woman, aged 25 years, who first complained of coryza, cough, fever, headache and pain in the back. A little later the neck became stiff and it became more and more difficult for her to turn in bed, her legs becoming paretic. The abdominal reflexes below the umbilicus disappeared and there was some hyperesthesia in the lower extremities. The fever continued, the lower extremities became completely paralyzed and irregular contractions appeared in the right arm and right half of the face. A lumbar puncture showed 1,100 cells per cubic millimeter, a majority of which were lymphocytes. The patient died one month after the onset of the symptoms. There was a diffuse meningomyelitis involving the whole cord. Harbitz said, "there may be doubt as to whether the symptoms depended on the changes in the cord itself or in the nerve roots and spinal ganglions; but it seems reasonable to assume that the changes in the membrane and the roots therein were the most important at the time as the changes in the cord itself, and with the marked edema, must have resulted in great functional disturbances. The edema may have been caused partly as the result of the inflammatory changes in the veins and resulting stasis, but it may also have been produced by toxic action from the great number of tubercles in the membranes."

Keschner and Davison (6) reported a case of a woman, aged 30 years, who developed lancinating pains in the right thigh and weakness in the right lower extremity. Neurological examination showed weakness of the left upper and right lower extremities which was most marked in the extensions of the foot. The deep reflexes were hyperactive, more so in the right lower extremity. There was a right Babinski sign. Sensory examination revealed hyperesthesia, hypalgesia and hypothermesthesia below the fourth dorsal dermatome, except in the perianal region in which sensation was normal. The spinal fluid contained 7 cells per cubic millimeter and a total protein of 41.5 mg. per cent. She had extensive pulmonary tuberculosis. Death occurred approximately one year following the development of pains in the thigh. The spinal cord showed extensive necrosis between the first and sixth thoracic segments. There was an accumulation of an inflammatory exudate in the subarachnoid space about the cord. The blood vessels of the meninges were thickened and their walls were infiltrated by inflammatory cells. The lumina of some of the vessels were obstructed. Keschner and Davison (6) said, "the spinal cord was subjected to two types of changes: (*1*) perivascular infiltrations, thickened adventitial coats and compression of the vessels and cord by the abscess, leading to vascular obstruction; (*2*) a direct invasion of the spinal cord at its margins by the inflammatory process. The latter process was less extensive than the former."

Recently 2 cases of generalized tuberculosis with extensive necrosis of the spinal cord were studied in this laboratory. The significant clinical and pathological findings are as follows:

CASE REPORTS

Case 1: The patient was a colored woman, aged 21 years, who was delirious when brought to the hospital. Her husband stated that she was in good health until ten days previously, at which time she first complained of severe frontal headaches, general malaise, fatigue and a feverish sensation. There were vague pains and a feeling of tingling in the lower extremities. Her feet and legs were completely paralyzed five days before admission and two days later she lost control of the anal sphincter and had to be catheterized.

On admission her temperature was 103° F.; pulse 110; respiration 24; the blood pressure, systolic 125 and diastolic 75. She was completely disoriented. The neck was stiff and its flexion caused pain. There was a flaccid paralysis of both lower extremities. The muscles of the abdomen and thorax were also paralyzed. Sensation was absent below the level of the second intercostal space anteriorly and the level of the spines of the scapulas, posteriorly. There was some disturbance in sensation along the lateral surface of the right arm and forearm. The right patellar reflex was absent, the biceps, triceps, ulnar, radial and left patellar reflexes were active. Both upper and lower abdominal reflexes were absent. There was no Babinski or ankle clonus.

The cerebrospinal fluid showed 318 cells, of which 81 per cent were polymorphonuclear leucocytes and 19 per cent lymphocytes. The sugar was 31 mg. per cent and the total proteins were 295 mg. per cent. Acid-fast bacilli were cultured from this fluid. A cerebrospinal fluid Wassermann test was positive. The patient's condition declined rapidly and she died twelve hours following admission.

Necropsy findings: Postmortem examination was made five hours following death. The body was that of a poorly nourished, colored female about 20 years of age. The peritoneum was covered with numerous small tubercles and there was a small amount of yellow fluid within the abdominal cavity. Fibrinous and fibrous peritoneal adhesions were present. A similar tuberculous process was present on the right and left sides of the thoracic cavity. The mediastinal lymph nodes showed extensive caseation.

Numerous small tubercles were present in the lungs. Most of them were less than 0.5 cm. in diameter. There were no cavities in the lungs. Microscopically the tuberculous lesions showed both the exudative and proliferative types of reaction. Similar tuberculous lesions were present in the liver and spleen. No acid-fast bacilli were found in these tissues.

The brain weighed 1,437 g. Its superior surface was hyperemic and covered by a slightly cloudy exudate. A thick purulent exudate covered the base of the brain. No changes were observed in multiple gross sections through the brain. The spinal cord, with its membranes, was removed from the cervical level downward. A thick purulent exudate covered the entire surface of the cord. It was thicker over the lumbar portion than over the cervical. Many sections were made through the cord. A focal area of necrosis 0.5 to 1.0 cm. in diameter was present in the upper portion of the thoracic cord. It was impossible in this area to recognize the gray and white tissue; however, anatomical structures could be recognized in the greater part of the cord. Smaller foci of necrosis were noted in different portions of the cord.

Histological observations on central nervous system tissue: Numerous foci of acute degeneration were present in both the gray and white matter of the cord. An irregular zone of necrosis was frequently found at the periphery (figure 1). The inflammatory exudate followed some of the blood vessels into the cord. No giant cells or areas of caseation were observed within the substance of the cord. The subarachnoid space was diffusely infiltrated with both mononuclear cells and polymorphonuclear leucocytes (figure

2A). An occasional giant cell was present. In the thoracic portion the dura mater was the site of a tuberculous reaction characterized by a localized area of caseation and epithelioid and giant cells. It is suggested that this may have been the site of an extradural abscess which extended inward to involve the cord. The nerve roots within the subarachnoid space were surrounded by the exudate and some were infiltrated with mononuclear cells (figure 2B). Groups of the nerve fibres were degenerated in many of these nerves (figure 3B). The wall of essentially every blood vessel was infiltrated with this exudate and their lumina were occluded by recent thrombi (figure 3A).

The meninges covering the brain exhibited changes similar to those about the spinal cord. Acid-fast bacilli were cultured from the spinal fluid.

FIG. 1. A portion of the periphery of the spinal cord showing the extensive degeneration of the myelin sheaths. A similar focal degeneration frequently occurred within the substance of the cord. Formol-thionin, myelin sheath stain.

Case 2: The patient was a colored male, 23 years of age, who said he had been in good health until three weeks before admission to the hospital. He was picking cotton when he suddenly became weak, developed a headache and had a severe pain in the epigastric region which radiated around to the back. He remained in bed following the onset of his illness. The headache persisted and there were attacks of nausea and vomiting. The patient thought he had fever. Approximately ten days following onset the patient noticed that he was unable to move his legs and that there was pain "under his knees and in the hips" when his lower extremities were moved. Two days before admission he was unable to void and the following day was catheterized.

On admission, five days preceding the time of death, the temperature was 103° F.; pulse 112; respiration 24; the systolic blood pressure was 120 and the diastolic was 80 mm. of mercury. He was acutely ill but coöperated satisfactorily during the examination. His weight was 130 pounds; this was 26 pounds less than his normal weight. There was

tenderness in the costovertebral area, bilaterally. There was a flaccid paralysis of both lower extremities. The cremasteric, lower abdominal and patellar reflexes were absent.

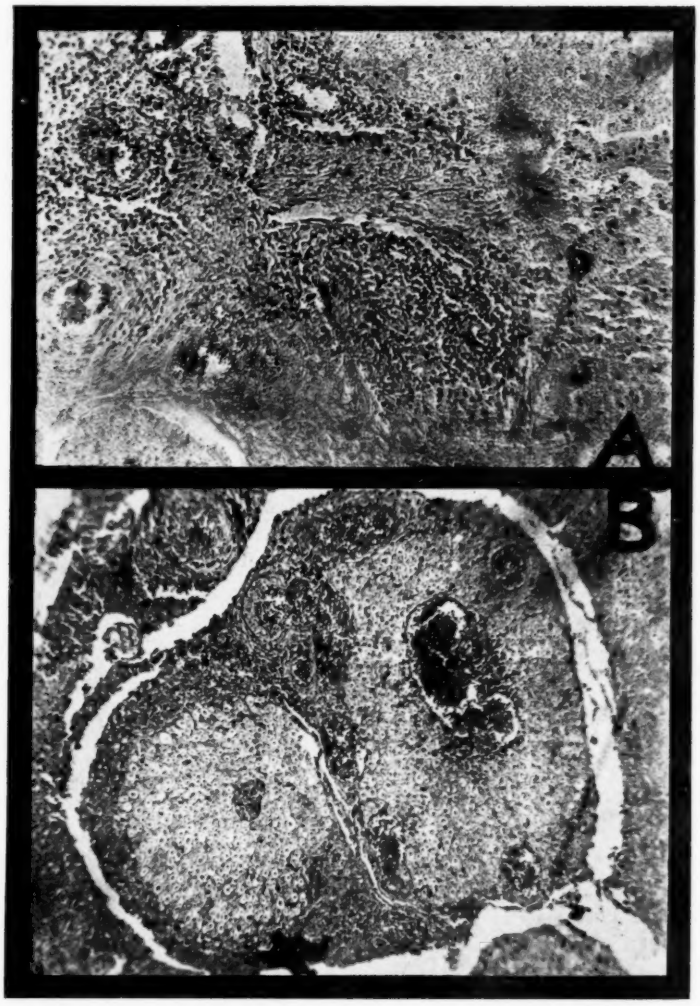

FIG. 2. A: Extensive necrosis and a cellular infiltration in the subarachnoid space. The former process was most extensive. Hematoxylin-eosin stain.

B: The inflammatory reaction surrounded and extended into many of the spinal nerves. Note the collection of mononuclear cells about the vessels in this nerve. Hematoxylin-eosin stain.

Ankle clonus, Kernig and Brudzinski reflexes were present. There was good tonus of the anal sphincter. The pupils reacted to light and accommodation.

The cerebrospinal fluid showed 186 cells, of which 78 per cent were lymphocytes and 22 per cent were polymorphonuclear leucocytes. The protein was more than 1,000 mg. per cent. The sugar was 26 and 48 mg. per cent on two occasions. Chlorides were 470

mg. per cent. Cultures were negative. The serological reactions were negative on both the blood and the spinal fluid.

The patient gradually became lethargic, then semicomatose and died five days following admission to the hospital.

Necropsy findings: The postmortem examination was made forty-eight hours following death. The body was that of a well developed and fairly well nourished young colored adult male. The serous cavities were free of fluid; however, there were extensive fibrous adhesions binding both lungs to the parietal pleura. The lungs were congested, especially in the posterior half. Small tubercles were present in the lower right lobe and on the pleural surface of this lung. No cavities were present. Several small tubercles were present in the spleen and liver. Microscopically more tubercles were found in the lungs

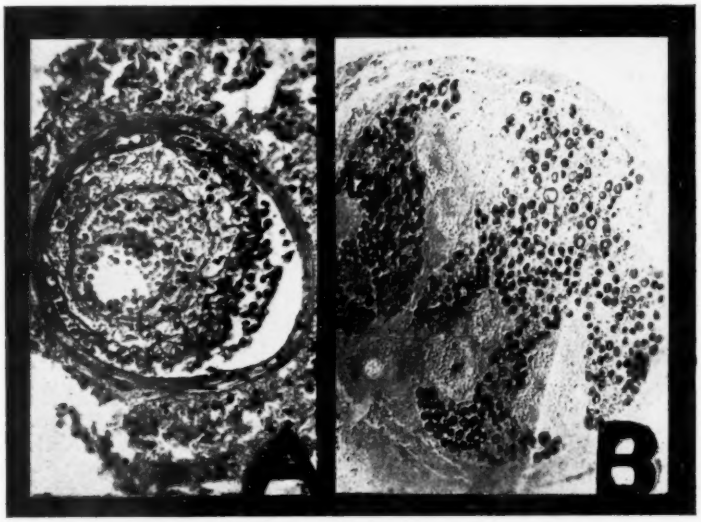

FIG. 3. A: The lumen of essentially every vessel about this spinal cord was occluded by recent thrombi. Sometimes the walls of those vessels were infiltrated by the inflammatory reaction. This shows one of the occluded vessels. Hematoxylin-eosin stain.

B: Extensive degeneration of the myelin sheaths was present in many of the spinal nerves. This shows an absence of myelin sheaths in focal areas within this nerve. Some of the remaining sheaths failed to stain as deep as the normal. Formol-thionin myelin sheath stain.

than were suspected from the gross examination. Tubercles were also found in the adrenals, lymph nodes and prostate. The tubercles in all the vicera were primarily of the proliferative type.

The urinary bladder contained approximately 1,500 cc. of urine. The bladder reached the level of the umbilicus.

The brain weighed 1,390 g. There was a gelatinous exudate over the base of the brain. A few tubercles were present along the lateral sides of the cerebral hemispheres. No pathological changes were observed in multiple sections through the brain except for many tubercles along the walls of the ventricles. The entire spinal cord was swollen and covered with a thick, gelatinous exudate. In the upper lumbar region of the cord there was a local area of enlargement which involved 1.5 cm. Approximately 4 cm. above this area

of swelling was one which involved 1.0 cm. of the cord. When the spinal cord was sectioned it was difficult to outline the gray and white matter in these two areas of enlargement. No definite tuberculoma was found within the cord.

Histological observations on central nervous system tissue: The lesions in the spinal cord were identical with those described in case 1. There were more lymphocytes in the inflammatory reaction in this than in the previous case. In one section there was a collection of tubercles between the pia and arachnoid in which there were several giant cells and epithelioid cells. The reaction here was very conspicuous in contrast to that elsewhere about the central nervous system. The tuberculous reaction was extensive about the base of the brain and in many sections the portion of the cortex adjacent to the surface was necrotic. A perivascular reaction accompanied many of the vessels as they extended down into the brain substance. Acid-fast organisms were demonstrated about the spinal cord.

DISCUSSION

It is obvious from the 2 case reports that both patients had a most extensive and wide-spread tuberculous involvement throughout their bodies. The transverse myelitis resulted from extensive necrosis which occurred in the upper thoracic region of the spinal cord in one and in the lumbar region in the second case. These areas of necrosis and the other focal areas of degeneration within the cord apparently resulted from the occlusions affecting the vessels in the subarachnoid space. The variation in the extent of the necrosis in the different segments of the cord, the involvement of both the white and gray substance, the absence of a specific tuberculous reaction within the cord and the location of a necrotic zone at the periphery of the white substance all may be explained adequately by the thrombotic occlusions of vessels surrounding the cord.

The greater part of the inflammatory reaction in the meninges in these cases is similar to that described by Rich (2) in hypersensitive individuals. Vascular occlusions are characteristic lesions in this type of tuberculous reaction. One might consider this necrosis in the cord to be the direct result of the effect of tuberculous proteins on the medullary sheaths; however, in the absence of tubercles within the cord this appears to be unlikely. Furthermore, the pia mater is not always destroyed, even over those areas of necrosis within the cord, such as might be expected if the degeneration in the cord were the direct result of the tuberculous reaction in the subarachnoid space. If this necrosis in the cord were a part of a hypersensitive reaction it would seem that it would occur more frequently in cases of generalized tuberculosis.

The failure to observe any tuberculoma in the cord and any tuberculous involvement of the vertebrae apparently would eliminate primary mechanical pressure. Furthermore, the areas of necrosis were multiple and varied in size and location within the cord. A tuberculoma was not demonstrated within the central nervous system of these cases, such as Rich and McCordock (7) have described. The examination of this tissue, however, was not as minute as that by these investigators.

Focal areas of necrosis in the spinal cord have been observed by others in tuberculous meningitis in which occluded vessels were present (1, 4, 6). Cases

of softening of the cord with metastatic tumors have been reported (8, 9,10). In these cases the tumor masses produced obstruction to the circulation to cause the necrosis. Chung (11) points out that syphilitic thrombosis of the vessels of the cord is a most important single factor in causing the sudden onset of paraplegia. Keschner and Davidson (6) consider that atherosclerosis and syphilis are the two most common causes of vascular occlusions in the spinal cord; of these, syphilis is by far the most common. The pathological changes in the cord due to sclerosis of the spinal vessels are much less frequent than those in the brain due to disease of the cerebral vessels. Mackay (12) in 1939 discussed the problem of vascular occlusion and necrosis of the spinal cord in cases of chronic meningitis. Jaffe and Freeman (13) in 1943 published a review of spinal cord necrosis and softening of obscure origin.

The sudden onset of paralysis in necrosis of the spinal cord is interesting. Cadwalader (4) says that "no variation in the character of the development of spinal paraplegia could be more striking than is the onset of paralysis in acute softening of the spinal cord caused by obliteration of the spinal vessels." One of the cases reported by Greenfield and Turner (14) was characterized by a sudden onset of paralysis. A case of necrosis of the cord reported by Spiller (8) likewise had a sudden onset of clinical symptoms. The first patient reported in this study observed pain and tingling in the lower extremities ten days preceding death, and the lower extremities were completely paralyzed only five days before death. The second case observed weakness in the lower extremities and then paralysis approximately ten days following the onset of his illness.

It is seldom that one encounters 2 cases as similar as these. They were both colored, one a female, aged 21 years, and the other a male, aged 23 years. Both patients were considered to be well until the onset of illness, ten and thirty days previous to death. The onset of paralysis was sudden and involved the lower extremities. Both patients lost control of their urinary bladders, while one also lost control of the anal sphincter. Both cases had a wide distribution of tubercles throughout the viscera of the body. There were no cavities in the lungs of either. The histological reactions about the tubercles likewise were similar; in fact, the sections were so much alike that one case could be substituted for the other without anyone observing any significant difference.

SUMMARY

Two cases of transverse myelitis are reported in young colored adults who had generalized tuberculosis and tuberculous meningitis. The acute paralysis resulted from necrosis of the spinal cord produced by vascular occlusions resulting from the tuberculous reaction in the meninges and wall of the blood vessels about the cord.

Spinal-cord necrosis secondary to vascular occlusions has been observed frequently; however, this process occurring with tuberculous meningitis apparently is infrequent.

A vascular occlusion should be suspected in any case in which there is a sudden onset of paralysis.

SUMARIO

Comunícanse dos casos de mielitis transversa en jóvenes de color que padecían de granulia y meningitis tuberculosa. La parálisis aguda provenía de la necrosis de la médula espinal producida por oclusiones vasculares debidas a la reacción tuberculosa en las meninges y pared de los vasos sanguíneos perimedulares.

La necrosis de la médula raquídea secundaria a oclusiones vasculares ha sido observada frecuentemente, pero, aparentemente rara vez en conjunción con la meningitis tuberculosa.

Debe sospecharse oclusión vascular en todo caso en que se presente súbitamente parálisis.

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MANAGEMENT OF PRIMARY TUBERCULOSIS IN CHILDREN[1,2]

R. V. PLATOU

Your very presence here indicates your appreciation of and interest in programs for the control of tuberculosis, of which recognition and management of childhood forms play so important a part. Routine skin testing or roentgenological examination of children has been integral in most such programs. Physicians are increasingly cognizant of the simplicity, usefulness and objectives of these surveys. Simply because lesions of primary infection are admittedly impossible to demonstrate during life in the majority of cases, tuberculin testing has been and will undoubtedly continue to be the most satisfactory method for case-finding in children; modern improvements in technique have removed almost all vestiges of its objectionable features.

There is surprising lack of unanimity of medical opinion regarding management of positive reactors. Whereas all agree that a positive tuberculin test gives no valid information regarding type, activity, infectivity, duration or source of infection, altogether too many physicians are content to note merely that a child does not appear to be ill, that roentgenograms show either a typical primary complex or no lesion, and that a social worker or public health nurse is arranging for the conventional roentgenological study of environmental contacts. Though such complacency may be warranted for the majority of children who react to tuberculin, numerous exceptions in our own experience at Charity Hospital in New Orleans have caused real concern over this all too prevalent attitude.

Honored by an invitation to discuss management of primary tuberculosis in children, I undertook an analysis of all deaths from tuberculosis which occurred in our hospital during the last ten years. This analysis only served to aggravate my own chronic concern over oft-neglected aspects of management. These fresh data only add more weight to familiar contentions, but are entirely pertinent for brief review here. Nothing in this study lessened our respect for potential dangers of this ordinarily benign phase of tuberculosis. Even if effective means for eradication of tubercle bacilli were available, the ounce of prevention would still be worth more than the pound of cure.

From July, 1936 through June, 1946 there were 153 deaths among 784 recognized clinical cases of tuberculosis occurring in over 82,000 children admitted (table 1). In this same period there were 28,544 deaths from all causes, almost 8 per cent of which were in children. Tuberculosis accounted for 9.8 per cent of the total deaths, and it was startling to find that it was responsible for over 6 per cent of all deaths in children.

The distribution by age of these deaths from tuberculosis in children was compared with that occurring in the United States (1) and in the State of Louisiana

[1] From the Department of Pediatrics, Tulane University School of Medicine, and Charity Hospital of Louisiana at New Orleans, Louisiana.

[2] Condensation of an address presented before the Southern Tuberculosis Conference at Jacksonville, Florida, October 3, 1946.

(2) in 1944; the similarity of resultant curves (chart 1) was of course expected, with deviation toward a lower percentage of deaths in the older age group of our patients explainable by the fact that this study included children to age 12 only. The mean duration of terminal illness appeared to be shorter by all four criteria than we had anticipated (table 2). When contact was known, it always antedated symptoms by months or years. The first symptoms which could even retrospectively be attributed to tuberculosis were ordinarily mild and rarely led to medical examination until weeks or months had passed. Definite symptoms

TABLE 1

Tuberculosis in children—Charity Hospital, New Orleans

Ten-year period ending June 30, 1946

	TOTAL	CHILDREN	
		Number	Per cent
Admissions, all diseases			
White	247,085	40,872	16.5
Colored	279,863	41,565	14.9
Total	524,948	82,439	15.7
Admissions, tuberculosis			
White	4,540	268	5.9
Colored	3,620	516	14.2
Total	8,160	784	9.6
Deaths from all causes			
White	12,960	880	6.8
Colored	15,584	1,371	8.82
Total	28,544*	2,251**	7.90
Deaths from tuberculosis			
White	1,288	36	2.79
Colored	1,525	117	7.67
Total	2,813*	153**	5.45

* 9.8 per cent of all deaths were due to tuberculosis.

** 6.1 per cent of all deaths in children were due to tuberculosis.

characterizing the terminal episode had usually been present for about three weeks before medical examination and hospitalization. A strongly presumptive diagnosis of tuberculosis was justified in most patients at this time, and over 80 per cent of the children had expired within three weeks of admission.

The symptomatology of fatal forms of tuberculosis in children is well known and perhaps remarkable only for its monotonous and ominous similarity. The three most prominent symptoms for each patient were tabulated as they occurred chronologically. Table 2 contributes no great surprises, but it does reveal that even the commonest and most diagnostic features may be obscure, secondary in importance or late in appearance. The significant lesions accompanying these symptoms discovered by clinical and roentgenographic means and confirmed by

necropsy in over half the cases consisted of phthisis in 58, meningeal in 50 and miliary involvement in 41; besides these three predominant lesions, 21 others were described, making a total of 170 discernible tuberculous lesions among these 95 patients. The term phthisis was used here in the broadest sense, to include a wide variety of pulmonary consolidations, many indistinguishable during life from nontuberculous lesions. It is noteworthy that nontuberculous complications were encountered in the terminal illness of only 18 patients.

One hundred and fourteen of these 153 deaths occurred before the fifth year; chart 2 confirms the experiences of others regarding distribution of deaths during these early years. During the first year, most deaths occurred between the third

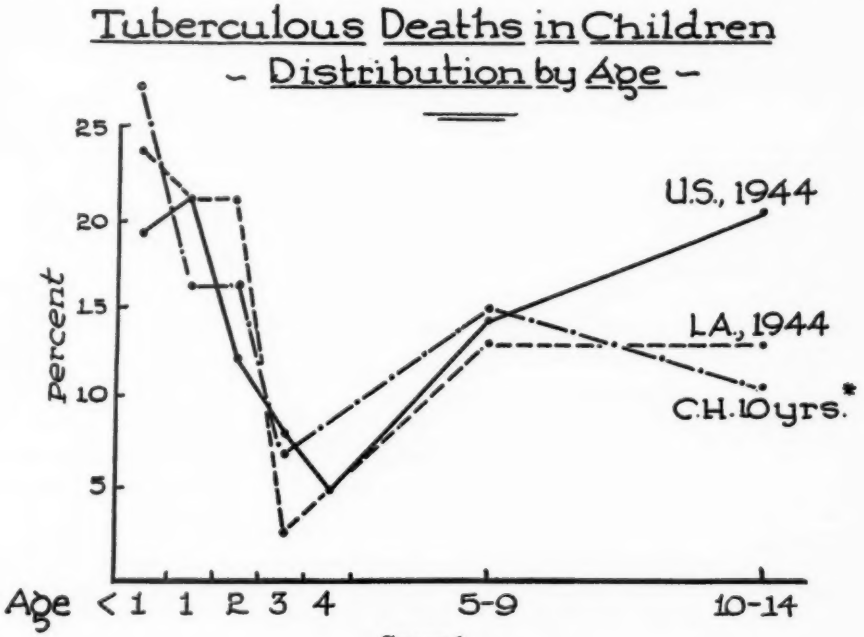

CHART 1

and ninth months. It seems reasonable to explain these curves by more intimate and continuous exposure of infants and toddlers rather than to invoke somewhat nebulous concepts of immunological immaturity.

The source of infection was known for only 26 of these patients and strongly suspected for 11 others. Among these 37, contacts were known to be with a single source in 30 instances and multiple in only 7. It was no surprise to learn that most of these were intimately exposed to open tuberculosis from earliest infancy. We discovered that known contact had existed before the third month of life in 18 patients and before the sixth month in 24. The age at first contact was beyond the sixth month or indefinite in the others. The contact was known to be very intimate, occurring daily during this period, in 24 of 37 for whom accurate data were available. Twenty-one of the contacts were known to have open

tuberculosis and 3 were said to have been arrested; we have not secured satisfactory information concerning the criteria by which the supposedly arrested status was established. Certainly, the development of a positive tuberculin test in an exposed infant is a far more delicate means of proving infectivity of a suspected or a supposedly arrested case than any other clinical or laboratory measures we can apply.

Our first knowledge of these appallingly long and intimate periods of exposure to open tuberculosis was secured at the time these patients were admitted for

TABLE 2

Tuberculosis in children

Features of terminal illness in 95 patients

Charity Hospital in New Orleans—ten years

A. Initial manifestations as they appeared chronologically

	FIRST	SECOND	THIRD	TOTAL
1. Fever	30	32	9	71
2. Cough	26	16	10	52
3. Intestinal	8	13	16	37
4. Meningeal	8	8	18	34
5. Weight loss	9	7	6	22
6. Glandular	3	2	1	6
7. Others	12	9	17	38

B. Duration of terminal illness

	FROM FIRST CONTACT	FROM FIRST SYMPTOM	BEFORE ADMISSION	IN HOSPITAL
Under 1 week			14	39
1–3 wks			38	40
1–3 mos	5	63	19	10
4–6 mos	2	17	11	2
7–12 mos	5	5	11	4
Over 1 yr	13	8		
Unknown	70	2	2	
Total	95	95	95	95

terminal hospitalization. In 20 of 37 patients, known duration of contact exceeded three months; in the others it lasted for a shorter or uncertain period. Other physicians or agencies may have made vigorous efforts to break such contacts, but from the meager data we have, this seems unlikely. Over two-thirds of these contacts were with one or both parents; the remainder were with grandparents or near relatives, and all but 2 were known to have occurred within the household. Whereas prolonged contact is not a necessary prerequisite for the development of fatal tuberculosis in infants and children, it certainly occurs in most instances and undoubtedly enhances the risk of such outcome.

Table 3 shows a consistently higher number of deaths in Negroes than in

whites. During the period of this study, 268 white children were admitted for clinical diagnosis of tuberculosis; 36 deaths among these represent a fatality rate of 13.4 per cent. In the same period 117 deaths occurred among 516 colored infants and children admitted for clinical diagnosis of tuberculosis, a fatality rate of 22.6 per cent. Explanations for these apparently disproportionate risks

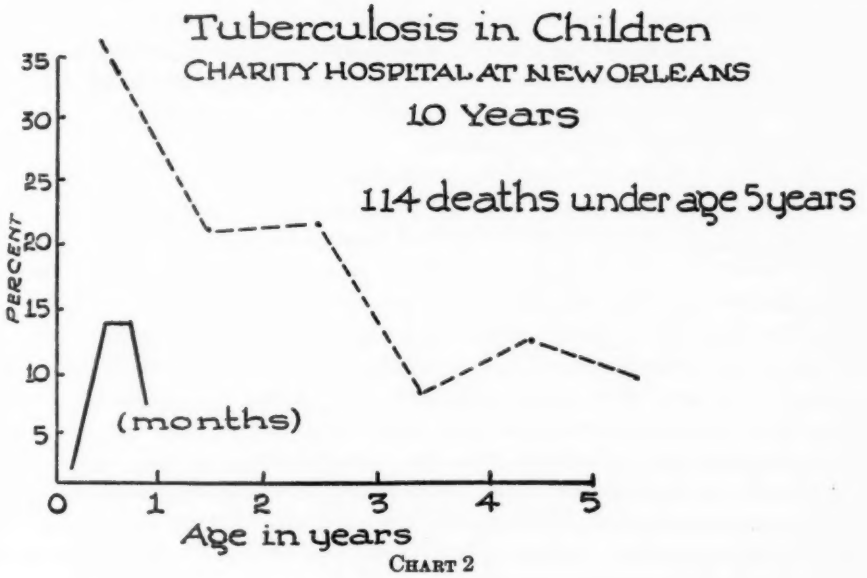

CHART 2

TABLE 3

Deaths from tuberculosis in white and colored children by age

AGE IN YEARS	WHITE	COLORED	TOTAL
Under 1	8	33	41
1	3	22	25
2	7	18	25
3	3	7	10
4	2	11	13
5–9	9	14	23
10–12	4	12	16
Total.....	36	117	153

for young Negro infants are not adequate at present. Thirty-three deaths in colored infants under one year represent 6.5 per cent of 516 admissions for tuberculosis in Negro children; in this same period only 8 white infants died, accounting for just 3 per cent of the total number of white patients. Sixty-eight per cent of all deaths in colored and 60 per cent of all deaths in white children occurred before the fourth year.

Recent experiences and observations, such as these, have further accentuated our anxiety over problems of prophylaxis, recognition and subsequent manage-

ment of *early* primary cases. Our studies indicate that routine premarital and prenatal tests for tuberculosis deserve at least equal weight with those for syphilis. Legislative action in the latter regard has effected a dramatic reduction in infantile forms of syphilis; perhaps a similar program would be equally effective in our attack on tuberculosis. The means are at hand, of proved merit and easily accomplished. Careful medical check-ups are a routine integral part of good obstetric practice; for reasons of maternal welfare these almost always include certain procedures for recognition of tuberculosis. In socio-economic circumstances favoring a high incidence of this disease, however, the advantages of such a program are frequently denied and, of course, it is in this unfortunate stratum that our most dismal experiences result.

Authoritative opinions regarding prognostic implications of early infection with tuberculosis are familiar to you all and only serve to intensify the concern I have previously expressed. The important reasons for such a dismal outlook are too well known to require repetition. There is no need at present for reopening the arguments regarding the relationship of allergy to immunity or entering into any controversy about implied protective virtues of a positive tuberculin test. I think we must all agree that, the earlier infection occurs, the more pessimistic and careful we must be in predicting its course. There is no place for complacency when one encounters a positively reacting infant or child.

The physician has at least six clear-cut responsibilities in this situation: he must classify or describe the lesion, judge activity, determine communicability, seek the source of infection, make recommendations for therapy based on specific objective data and, last, follow each patient carefully at frequent intervals at least until all evidences of activity have subsided or until resolution of the initial lesion is complete, as judged by discrete calcification. Certainly, the three-year period following the initial infection is most important. Careful classification or description is the best means for initiating his program; it is rank fallacy to believe that all asymptomatic tuberculin-positive children are necessarily in a benign category. Each patient must be studied carefully, and simple routine roentgenograms of the chest are not enough. Accepted, published nomenclature is familiar to most physicians; though weighted perhaps too heavily in favor of interpretation by roentgenographic means alone, it still has great merit.

Regardless of classification, activity must be measured by objective means we all use daily. Most of these, such as body temperature and weight, sedimentation rate of erythrocytes, total and differential leucocytic count and the ratio of monocytes to lymphocytes, can be influenced by a multitude of diseases other than tuberculosis. We often encounter clinical situations in which it is impossible to establish or differentiate causes for aberrations from normal values. When this occurs, the positively reacting child always deserves the benefit of doubt; evidences of activity should be ascribed to infection with tuberculosis until proved due to other cause.

When there are symptoms or evidences of activity attributable to tuberculosis of any form—primary or reinfection—an attempt should always be made to assess hazard to others. No exception is justified simply because we believe most cases classed as primary, meningeal or miliary are for practical purposes non-

communicable. Demonstration of acid-fact bacilli in sputum, gastric washings or feces constitutes a firm basis for inistituting precautions well known to all medical workers.

We have repeatedly emphasized that as much, if not more, information can be gained by close questioning of patients or parents regarding probable contacts than by simply suggesting that conventional roentgenological studies be done. Following such perusal for the most likely contacts, routine tuberculin testing will favor more intelligent and economic use of roentgenological aids.

Limitations of the purely roentgenological method of case-finding are well known. Although roentgenograms play an all-important rôle in objectively discovering and delineating tuberculous lesions, they will never be accurate enough to supplant sound medical judgment. I raise this small voice not to decry the remarkable and praiseworthy strides that have been made toward increasing use of this instrument, but only to slow the tide of opinion implying that it may think, feel and hear as well as it sees!

Specific recommendations should follow logically when the case in question has been properly classified, activity and communicability assessed and contacts determined. It seems unnecessary to stress once again that doubtful features should be considered tuberculous until proved otherwise, that close supervision and frequent evaluation of activity are most important for three years following infection, and that specific means are at our disposal for preventing, avoiding or significantly attenuating each and all of the common hazards that arise during childhood. Most serious of these is reinfection or continuous contact, particularly during three years after the initial infection and during adolescence. Such factors as malnutrition, excessive fatigue, inhalation anesthetics and intercurrent diseases, particularly pneumonia, pertussis and measles, are equally well known.

The diligence of follow-up care must of course be individualized. Complete rest, modified or full activity should be justified by criteria of activity previously discussed. Discernible lesions should be reëxamined at frequent intervals at least until resolution or discrete calcification has occurred. During this time all the talents of physician, nurse and social worker should be directed at correction of environmental causes, prevention of exogenous reinfection, maintenance of rest during any evidence of active infection, improvement of nutrition and physical condition and prevention or attenuation of dangerous intercurrent nontuberculous infections.

Therapy for the primary infection is still nonspecific, employing well known concepts of protection from reinfection, rest as indicated by specific criteria, maintenance of the best possible nutritional status and education of patients and all members of their families in the nature of the disease and effective means for controlling its spread. Closer attention to time-proved measures can still further reduce the dangers of tuberculous infection in children until specific means for its eradication are available. It has been amply demonstrated that all our diligence and judgment directed at the control of primary tuberculosis are rewarded by a decreasing experience with some of the most desperate clinical problems in pediatrics.

SUMMARY

In an analysis of all deaths from tuberculosis at Charity Hospital of Louisiana at New Orleans during the last ten years, it was found that 9.8 per cent of the total deaths and 6 per cent of all deaths in children were attributable to this disease. Distribution of deaths by age and color, symptomatology, source of infection, features and duration of the terminal illness was tabulated. These studies accentuate our anxiety over problems of prophylaxis, recognition and management of *early* primary cases.

When a physician encounters an infant or child with a positive tuberculin test, he has six clear-cut responsibilities: he must classify or describe the lesion, judge activity, determine communicability, seek the source of infection, make recommendations for therapy based on specific objective data and, last, follow each patient carefully at frequent intervals at least until all evidences of activity have subsided or until resolution of the initial lesion is complete.

Therapy for the primary infection is still nonspecific, employing well known concepts of protection from reinfection, rest as indicated by specific criteria, maintenance of good nutritional status and education of patients and all members of their families in the nature of the disease and effective means for controlling its spread.

SUMARIO

En un análisis de todas las muertes debidas a tuberculosis en el Charity Hospital de Louisiana de Nueva Orleans durante el último decenio, se observó que 9.8% de todas las muertes y 6% de todas las infantiles eran imputables a dicha dolencia. Tabuladas las muertes conforme a edad y color del enfermo, semiología, fuente de infección, características y duración de la enfermedad terminal, acentuáse la ansiedad infundida por los problemas de profilaxia, reconocimiento y atención de los casos primarios *tempranos*.

Cuando el médico encuentra a un lactante o niño con una reacción positiva a la tuberculina, tiene seis obligaciones bien definidas: debe clasificar y distribuir la lesión, justipreciar la actividad, determinar la trasmisibilidad, buscar las fuentes de infección, formular recomendaciones terapeúticas basadas en datos específicos, y por fin, observar al enfermo cuidadosa y frecuentemente por lo menos hasta que hayan desaparecido todos los signos de actividad o hasta que se complete la resolución de la lesión inicial.

La terapeútica de la infección primaria es todavía anespecífica, utilizándose los conocidos conceptos de protección contra la reinfección, el reposo según lo indican pautas específicas, el mantenimiento de un buen estado nutritivo y la instrucción de los enfermos y de todos los familiares en la naturaleza de la enfermedad y en los medios más efectivos para cohibir su propagación.

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PULMONARY FUNCTION FOLLOWING PNEUMOTHORAX[1,2]

An Investigation of the Volume and Ventilation of the Lungs

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A relatively long time after the therapeutic value of pneumothorax treatment had gained general recognition, investigations were made of its physiological effect. In Germany these questions have been dealt with, among others, by Anthony and his coworkers, and in the United States especially by Cournand and Richards and coworkers. Very few investigations were made of pulmonary function after the conclusion of pneumothorax treatment. Cournand and Richards (1) carried out such investigations in 11 cases, which, on an average, showed a moderately reduced function. Potter (2) made a clinical study of the state after the conclusion of pneumothorax treatment and found fairly often X-ray changes in the form of thickened pleura, but more rarely functionally significant changes.

It is not unusual for a patient who has received pneumothorax treatment for pulmonary tuberculosis to be more troubled with dyspnea after the treatment than before. Especially is this the case if a pleurisy with effusion arose during the treatment and led to an obliterative pleuritis with retraction of the lung. If such changes are bilateral, the dyspneic state may be very troublesome and sometimes lead to complete invalidism. In connection with certain forms of pulmonary tuberculosis, dyspnea is common also without pleural complications, and in single cases it may often be difficult to determine the real cause of the dyspneic tendency.

Theoretically there are several alternatives that may give rise to the diminished respiratory reserve in such cases. The following causes are chiefly to be reckoned with:

1: Diminished available amount of parenchyma owing to the pathological process.
2: Development of emphysema of the so-called compensatory type owing to contraction of the pathological foci.
3: Changes involving reduced ventilatory efficiency of the uninvolved parenchyma (ventilatory insufficiency).

The first of these factors is generally reckoned with, but the second, compensatory emphysema, has come to occupy a very obscure place as a cause of respiratory insufficiency in pulmonary tuberculosis. When closer attention is paid to this factor, one finds that the majority of patients with chronic pulmonary tuberculosis are more or less affected by it, not infrequently with important consequences to their respiration. Finally, the changes leading to impaired ventilation are caused both by pleural retraction of the lung following pneumothorax treatment and by the tuberculous process in the lung.

In order to try to throw light on the quantitative importance of the functional

[1] From the Medical Tuberculosis Department, St. Göran's Hospital, Stockholm, Sweden.
[2] This study was made under a grant from the Swedish National Union against Tuberculosis.

impairment, often following in the wake of pneumothorax treatment, the following patients were studied:

(*a*) 11 cases with completed pneumothorax treatment and with more or less prominent parenchymal and pleural changes, and

(*b*) 25 patients with pleurisy with effusion who received pneumothorax treatment but who had no demonstrable parenchymal lesions, either before or after the treatment, and who, judging by the course of the disease, have complete pleural obliteration.

It should be possible in this way to get an idea of the impairment of function that may be caused solely by pneumothorax treatment when this has resulted in pleural obliteration and retraction, although the pleural changes in patients with pulmonary tuberculosis treated with pneumothorax are often considerably greater owing to the length of treatment, the nature of the effusion, etc. Pneumothorax treatment in cases of exudative pleuritis has, for some years, been tried in Sweden with the aim of attempting to reduce the large number of cases that later develop pulmonary tuberculosis. The results of this treatment, as compared with those of conservative treatment, are not yet clear.

METHOD

In order to study the functional reserve of the lungs, certain elementary physiological data were investigated; namely, the pulmonary volumina of the lung and the respiratory dead-space.

Other methods are available, but those employed here are sensitive tests that generally refer exclusively to the state of the lungs. They are, moreover, easily reproducible and are practically independent of the coöperation of the patient. Cournand and Richards (1, 3, 4) and Cournand and Berry (5) achieved good results with tests of the maximum breathing capacity, breathing reserve and their relation to each other. Although they do not fulfil the demands mentioned above, these tests are sufficiently encouraging to suggest further attempts along similar lines. Of the methods employed by these authors (6), the "pulmonary emptying rate," that is, the rapidity with which, during the inhalation of oxygen, the lungs eliminate nitrogen, is of particular interest as a criterion of the effectiveness of ventilation. It has important points of contact with the present writer's method for the estimation of the dead-space.

In the present investigation no working test has been employed, but it is doubtless along this line that tests of function will in future develop; study of the blood gases may be more informative than in the state of rest, when they may be normal, even in the presence of far advanced lesions.

As has been shown, among others, by Bohr (7), Lindhard (8), Christie (9), Hurtado and Boller (10), there is a definite relation between the various lung-volume components, which for normal individuals lies within rather narrow limits.[3] Hurtado and his coworkers, during the 1930's, published a number of

[3] The normal value, as found by the author (11) with the present method, for the share of the total volume (= lung volume on maximal inspiration) taken by the residual air (= lung volume on maximal expiration) was for men 22.7 per cent ± 2.5 and for women 25.5

papers on pulmonary volumina and their variations under normal and pathological conditions; they studied ventilation in emphysema and pneumonoconiosis (12, 13). They came to the conclusion that the relation between the residual and total capacity was a reliable indicator of respiratory efficiency. The higher this ratio was, the more marked was dyspnea. The present writer (11) was able to confirm this and also found that the same applies to the equilibrium capacity, and not only in emphysema but in all cases of impaired pulmonary function with tendency to dyspnea.

The author found that high ratios for (*1*) residual air over total volume and (*2*) equilibrium capacity over total volume are most frequently caused by inadequately ventilated portions of the lungs, in which, therefore, respiration is insufficient. This occurs in bronchiectasis, emphysema, in fibrotic or infiltrated parenchyma, in cavities, etc.

With the decrease of the lung volume during pneumothorax treatment, the normal relation between the subdivisions of the pulmonary volumina was retained, unless some large part of the lung was badly ventilated because of pleural adhesions or some other cause. It was, therefore, possible to establish a hypothesis implying that under various conditions the organism strives to retain the normal relations between the effective subdivisions of the lung. When functionally inferior air-spaces (cavities, infiltrated, indurated or emphysematous parts, etc.) are added to these effective volumina the result will be a raising of the relation between the parts in question and the whole. Such a rise is tantamount to impaired pulmonary function, and it is associated, as has been mentioned above, with a more or less pronounced tendency to dyspnea. Thus, if the absolute values of the pulmonary volumina indicate the quantitative measure of the lung volume investigated, the relative values give an indication of its ventilatory quality.

In so far as completed pneumothorax treatment entails any changes of the kind mentioned above (hypoventilation of certain parts through reduced mobility of the thorax and the diaphragm), it ought to be possible to demonstrate this by measuring pulmonary volumina. The absolute values, such as the vital and the total capacity, must also be of interest.

In addition, the respiratory dead-space has been determined according to the author's method (11) in order to ascertain the efficiency of ventilation under these conditions.[4] The author has been able to show that an uneven ventilation, with the method used, has the same effect on the value for the dead-space as a real increase of the same.

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per cent ± 2.8, while the corresponding values of the equilibrium capacity (= lung volume following a normal expiration) taken by the tidal air were 48.4 per cent ± 5.0 and 46.3 per cent ± 6.0, respectively.

[4] Eleven determinations of the dead-space carried out on 8 men yielded a mean value of 0.18 lt. (37° C., moist). The values varied between 0.13 and 0.26 lt. For women (5 determinations) a mean value of 0.11 lt., with a variation of the values between 0.09 and 0.14 lt., was obtained. The dead-space varied between 18 and 45 per cent of the tidal air, but was as a rule about 30 per cent. In cases with emphysema this figure generally exceeded 50 per cent; a value above this limit must be regarded as pathological.

The fasting patients were examined in a comfortable sitting position in the morning after a rest of about half an hour. After the vital capacity was determined, the equilibrium capacity was obtained in the following way: A mixture of hydrogen gas of known concentration and volume in a closed respiratory system with motor-driven circulation was allowed during ordinary, quiet breathing to distribute itself between the patient's lungs and the spirometer system. At intervals of exactly one minute, samples of the content of the spirometer were taken and analyzed for hydrogen. When a practically complete mixture of the gas was obtained and calculated volume of gas in the lungs was thus constant, the mean value of at least 3 samples was taken as the definitive measure of the volume of the lungs. For hydrogen-gas analysis the combustion method was used and a standard deviation for each determination of the lung volume of 89 ±19 cc. was obtained.

With the help of the values for the lung volume that were obtained every minute, it was possible to follow the course of the mixing of the intrapulmonary air with the gas of the spirometer system. As the other factors affecting this course were known, it was possible to calculate the dead-space that would give rise to such a course of mixing.

The accuracy of this dead-space value varied, but in normal cases it was correct to within 0.01 to 0.02 lt. In cases with higher dead-space values, the limits of variation were greater.

For further details of the method the reader is referred to the original paper (11).

MATERIAL

The material examined comprises mainly patients from the medical tuberculosis department of St. Göran's Hospital.

Eleven of these patients had undergone pneumothorax treatment for pulmonary tuberculosis, 5 of these 11 having had pneumothorax on both sides. In several cases pleural effusion complicated the course of the treatment, and retraction of the lung often arose with—or even without—this cause. The nature of the parenchymal lesions varied, but the majority suffered considerable restriction of the functioning amount of parenchyma. Three patients had compensatory emphysema, confirmed in 2 cases on postmortem examination (cases 3 and 10). The cases are described in the case reports.

The other 25 patients had pleurisy with effusion without parenchymal changes; they had received so-called preventive pneumothorax treatment, usually for a period of one to two years, but in 9 of the cases the treatment was broken off earlier on account of obliterative pleuritis. In the majority of cases the treatment was carried out during the years 1942 to 1944. In 21 cases complete or almost complete collapse of the lung was obtained to start with, but 4 cases had, from the outset, such adhesions that the collapse was only moderate. The retraction of the lung that resulted in these 25 cases was not so pronounced as one sees in certain patients with pneumothorax treatment for pulmonary tuberculosis; it was generally restricted to obliteration of the costophrenic sulcus or a horizontal diaphragm with lateral fixation to the thoracic wall. More marked thickening of the pleura or greater retraction of the mediastinum to the treated side were seldom found. At the termination of treatment, the majority seems to have had complete obliteration of the pleural space.

RESULTS

A. *Pulmonary tuberculosis with completed pneumothorax treatment:* The cases investigated were purposely chosen to cover a wide variety of type and it will,

therefore, be necessary to describe them more in detail (table 1). Cases 1 and 4 had rather small lung lesions, and the pleural thickening was relatively slight, especially in case 1. In agreement with this, the absolute values of the pulmonary volumina were normal for the size of the body or only slightly diminished. One, therefore, expected a fairly normal function, and none of these patients suffered from dyspnea. In full agreement herewith, a normal value was found for the dead-space in case 4, where it was possible to determine it. In case 2, there was evident emphysema of compensatory type, which gave rise to the typical increase of the residual air, both as regards its absolute and relative values. The impaired function was clearly shown in the increased value of the dead-space. Dyspnea was a prominent symptom in this patient.

With the exception of cases 6 and 7, all the other cases showed a more or less pronounced tendency to dyspnea. To some extent this was probably due to far advanced parenchymal lesions but, especially in cases 9, 5 and 11, impaired ventilation (note the low vital capacity) was probably caused by bilateral pleural retraction, following pneumothorax. In case 9 there was an especially large dead-space indicative of emphysema.

Apart from the obviously pathological dead-space values in patients with emphysema (cases 2 and 9) the other cases showed no considerable deviation from the normal, though a certain rise of the absolute values may very well exist in the women. The relative dead-space value, which is normal, invites caution in interpretation.

As appears from table 1, the majority of the cases showed a definite decrease of the total lung volume and the vital capacity, as well as a very marked rise in the relative values of the residual air and equilibrium capacity. These rises indicate a markedly reduced function in accordance with the tendency to dyspnea. Although in certain cases it may be assumed that this impairment of function is largely due to the pleural changes, it is not possible to determine quantitatively the extent to which they have contributed to the impairment. A more detailed discussion of this point in connection with certain typical cases is given under the heading "Discussion."

B. *Completed pneumothorax treatment in cases of pleurisy with effusion without parenchymal lesions:* In order to decide whether the values of the pulmonary volumina are normal or not, a comparison is often made with calculated values. These values were calculated on the basis of the subject's body surface (which has been regarded as a function of height and weight (West (14)), his basal metabolic rate (Anthony (15)), or simply of his height or weight. The uncertainty of these calculations is considerable and a more reliable method is to compare the group presented here with a group of healthy persons. The latter procedure was applied in the present study. A group of healthy persons between the ages of 20 and 40, who had been previously examined (Birath (11)), were taken as the normal material.

The results of the investigations of the lung volume and its subdivisions in cases of pleurisy without parenchymal lesions are given in table 2.

The single cases in this group showed, on the whole, no considerable deviations from the normal which, on account of the relatively slight postpleuritic changes,

TABLE 1

Absolute and relative values of the pulmonary volumina and the dead-space value in 11 cases of pulmonary tuberculosis (5 males and 6 females) with completed pneumothorax treatment

CASE NUMBER	PULMONARY VOLUMINA						DEAD-SPACE VALUES		
	Absolute values in liters (37°C., moist)				Relative values in per cent of the total volume		Absolute values in liters (37°C., moist)		Relative value per cent of the tidal volume
	Equilibrium capacity	Residual air	Vital capacity	Total volume	Equilibrium capacity	Residual air	Dead-space	Tidal air	
Males									
1	3.76	1.74	5.36	7.10	53.0	24.5			
2	3.04	2.18	2.64	4.82	63.1	45.2	0.47	0.84	56.0
3	2.80	1.90	2.59	4.49	62.4	42.3			
4	2.33	1.07	3.58	4.65	50.1	23.0	0.15	0.43	34.9
5	1.81	1.48	1.14	2.62	69.1	56.5			
Females									
6	2.70	1.72	2.78	4.50	60.0	38.2			
7	2.59	1.70	2.86	4.56	56.8	37.3	0.14	0.42	33.3
8	2.44	1.48	2.14	3.62	67.4	40.9	0.18	0.53	34.0
9	1.46	0.98	1.57	2.55	57.3	38.4	0.32	0.44	72.7
10	1.42	1.24	0.87	2.11	67.3	58.8			
11	1.41	1.15	0.97	2.12	66.5	54.2	0.18	0.42	42.9

Case reports for table 1

Case 1: Terminated pneumothorax treatment for pleurisy with effusion on the right side with moderately advanced apical phthisis on the left. Obliteration of the right costophrenic sulcus. No dyspnea.

Case 2: Chronic contracting apical phthisis on the right side with a cavity the size of a walnut and scattered, fibrous foci. Considerable emphysema. Obliteration of the right costophrenic sulcus after pneumothorax treatment. Dyspnea ++.*

Case 3: Bilateral contracting apical phthisis with cavitation. Moderate emphysema (verified at autopsy). Considerable pleural thickening on the left and obliteration of the right costophrenic sulcus after bilateral pneumothorax treatment and effusion on the right. Dyspnea ++.*

Case 4: See figure 5.

Case 5: See figure 1.

Case 6: Chronic contracting apical phthisis with cavities. Obliteration of the right costophrenic sulcus and moderate pleural thickening after pneumothorax treatment with effusion. Dyspnea +.*

Case 7: Moderately advanced apical phthisis on the right side. Obliteration of the costophrenic sulcus after pneumothorax with effusion. Dyspnea +.*

* Dyspnea + = Moderate dyspnea on movement.
* Dyspnea ++ = Dyspnea even on slight exertion.

TABLE 1—*continued*

Case 8: See figure 2.

Case 9: See figure 4.

Case 10. Far advanced, bilateral phthisis with cavities, localized mainly in the apices. Marked pleural thickening (exudate) over the left apex. Obliteration of the costophrenic sulci after bilateral pneumothorax treatment. Moderate emphysema (verified at autopsy). Dyspnea +++.*

Case 11: See figure 3.

* Dyspnea +++ = Dyspnea even at rest.

was not expected. In one single case (case 20), surprisingly high relative values were obtained (table 2). Experience has shown that such surprises are sometimes met with, especially in the case of uneasy and "nervous" female patients. These values are probably due to a heightened respiratory level and incomplete expiration caused by nervousness during the examination.

A group comparison with the normal material (tables 3 and 4) shows that the total capacity is diminished, both for the men (by about 23 per cent) and for women (by about 11 per cent). The same applies to the vital capacity (men, 27 per cent and women, 13 per cent). The equilibrium capacity, on the other hand, both for the women and the men, was not definitely changed. The residual air, again, was for the women about 22 per cent lower than the normal, but for the men it was not definitely diminished.

A statistical analysis was carried out separately for the men and women.

The differences between the values for normal women and the postpleuritic group are shown in table 3. A statistically significant difference is found only in respect to the residual air, where the difference is equal to three times its standard error; but there was also a difference, which was probably of statistical significance in regard to the vital and the total capacity, where the difference exceeded two but not three times its standard error.

Since there were only 7 males, the classical method was not used for the statistical calculation, but instead, variance analysis (Snedecor's F-test). In this connection, it was proved that the probability (P) that a difference between the values was due to mere chance is, for the residual air, > 0.2, indicating no significant difference; and for the equilibrium capacity, $0.05 < P < 0.2$, which is a statistically uncertain difference. For the vital and the total capacity the difference is statistically significant; in both cases $P < 0.001$ (table 4).

Concerning the relative values, the male cases showed an obvious increase in the ratio $\frac{\text{Residual capacity}}{\text{Total capacity}}$ and the female cases a slight tendency to increase, as compared with the normal values (tables 3 and 4). This tendency was confirmed by the more evidently increased values for the ratio $\frac{\text{Equilibrium capacity}}{\text{Total capacity}}$,

since an increase of one of these ratios was quite regularly followed by an increase of the other.

TABLE 2

Absolute and relative values of the pulmonary volumina and the dead-space value in 25 post-pleuritic cases (7 males and 18 females) with completed pneumothorax treatment

CASE NUMBER	PULMONARY VOLUMINA						DEAD-SPACE VALUES		
	Absolute values in liters (37°C., moist)				Relative values in per cent of the total volume		Absolute values in liters (37°C., moist)		Dead-space in percentage of tidal air
	Equilibrium capacity	Residual air	Vital capacity	Total volume	Equilibrium capacity	Residual air	Dead-space	Tidal air	
Males									
12	4.30	2.17	4.46	6.63	64.9	32.7			
13	3.14	1.34	4.54	5.88	53.4	22.8	0.24	0.59	40.7
14	2.85	1.64	3.39	5.03	56.7	32.6	0.27	0.63	42.9
15	2.68	1.14	4.09	5.23	51.2	21.8			
16	2.59	1.44	2.88	4.32	60.0	33.3	0.16	0.42	38.1
17	2.03	1.01	2.99	4.00	50.8	25.3	0.25	0.46	54.3
18	1.68	1.00	3.45	4.45	37.8	22.5			
Mean.....	2.75	1.39	3.69	5.08	51.7	27.3			
Females									
19	2.98	1.48	4.03	5.51	54.1	26.9	0.18	0.44	40.9
20	2.86	2.33	1.69	4.02	71.1	58.0	0.17	0.41	41.5
21	2.78	1.38	3.50	4.88	57.0	28.3	0.13	0.51	25.5
22	2.73	1.30	3.07	4.37	62.5	29.7	0.31	0.67	46.3
23	2.73	1.47	3.82	5.29	51.6	27.8	0.10	0.44	22.7
24	2.57	1.14	3.77	4.91	52.3	23.2			
25	2.47	1.47	3.45	4.92	50.2	29.9	0.32	0.59	54.0
26	2.32	1.23	3.22	4.45	52.1	27.6	0.34	0.66	52.0
27	2.26	0.73	3.11	3.84	58.9	19.0			
28	2.24	1.04	3.30	4.34	51.6	24.0	0.22	0.53	41.5
29	2.13	1.01	3.40	4.41	48.3	22.9			
30	2.13	1.13	3.50	4.63	46.0	24.4	0.14	0.29	48.3
31	1.95	0.72	3.11	3.83	50.9	18.8			
32	1.91	1.13	2.95	4.08	46.8	27.7			
33	1.63	1.03	2.55	3.58	45.5	28.8			
34	1.51	0.62	3.22	3.84	39.3	16.1			
35	1.36	0.77	1.80	2.57	52.9	30.0			
36	1.26	0.90	2.22	3.12	40.3	28.8			
Mean.....	2.21	1.16	3.10	4.26	53.5	27.3			
Standard error of the mean.	±0.12	±0.09	±0.15	±0.17	±3.2	±2.0			

The difference between normal men and the cases under investigation in regard to the ratio $\frac{\text{Residual air}}{\text{Total capacity}}$ is most likely statistically significant, because covari-

ance analysis shows that: $0.001 < P < 0.01$. As regards the women, however, it was not possible to establish a statistically significant difference ($P > 0.2$). Between the women under investigation and normal women a statistically most likely significant difference exists for the ratio $\frac{\text{Equilibrium capacity}}{\text{Total capacity}}$, since: $0.001 < P < 0.01$. For men this difference was only probably significant, since: $0.01 < P < 0.05$. (See chart 1.)

TABLE 3

Differences between mean values of the pulmonary volumina in 19 normal and 18 postpleuritic patients (females)

CASES (FEMALES)	ABSOLUTE VALUES IN LITERS (37° C., MOIST)				RELATIVE VALUES IN PER CENT OF THE TOTAL VOLUME	
	Equilibrium capacity	Residual air	Vital capacity	Total volume	Equilibrium capacity	Residual air
Normal (19)....	2.22 ±0.11	1.49 ±0.06	3.57 ±0.10	4.79 ±0.15	46.3 ±1.4	25.5 ±0.7
Postpleuritic (18).....	2.21 ±0.12	1.16 ±0.09	3.10 ±0.15	4.26 ±0.17	53.5 ±3.2	27.3 ±2.0
Difference and ± standard error of the difference...	0.01 ±0.16	0.33 ±0.11	0.47 ±0.18	0.53 ±0.23	−7.2 ±3.49	−1.8 ±2.12

TABLE 4

Differences between mean values of the pulmonary volumina in 16 normal and 7 postpleuritic patients (males)

CASES (MALES)	ABSOLUTE VALUES IN LITERS (37° C., MOIST)				RELATIVE VALUES IN PER CENT OF THE TOTAL VOLUME	
	Equilibrium capacity	Residual air	Vital capacity	Total volume	Equilibrium capacity	Residual air
Normal (16)....	3.18 ±0.11	1.49 ±0.06	5.08 ±0.12	6.57 ±0.15	48.4 ±1.2	22.7 ±0.6
Postpleuritic (7).....	2.75	1.39	3.69	5.08	51.7	27.3
Difference....	0.43	0.10	1.39	1.49	−3.3	−4.6

The results were also grouped according to the character of the roentgenologically demonstrable pleuritic changes. The first group comprised those cases which, following pneumothorax treatment, showed only slight residual pleurisy, such as obliteration of the costophrenic sulcus, possibly in combination with somewhat thickened pleura and, in some cases, minor apical pleural thickening (14 cases). In the second group were those cases in which, due to adhesions to the thoracic wall, the diaphragm had assumed a practically horizontal position (4 cases). The third group comprised the 7 cases with the greatest changes, but even these showed only moderate pleural retractions.

A comparison between the first and the third group showed that a reduction

of all capacities had taken place in the third group, while the relative lung-volume values did not show any differences between the groups.

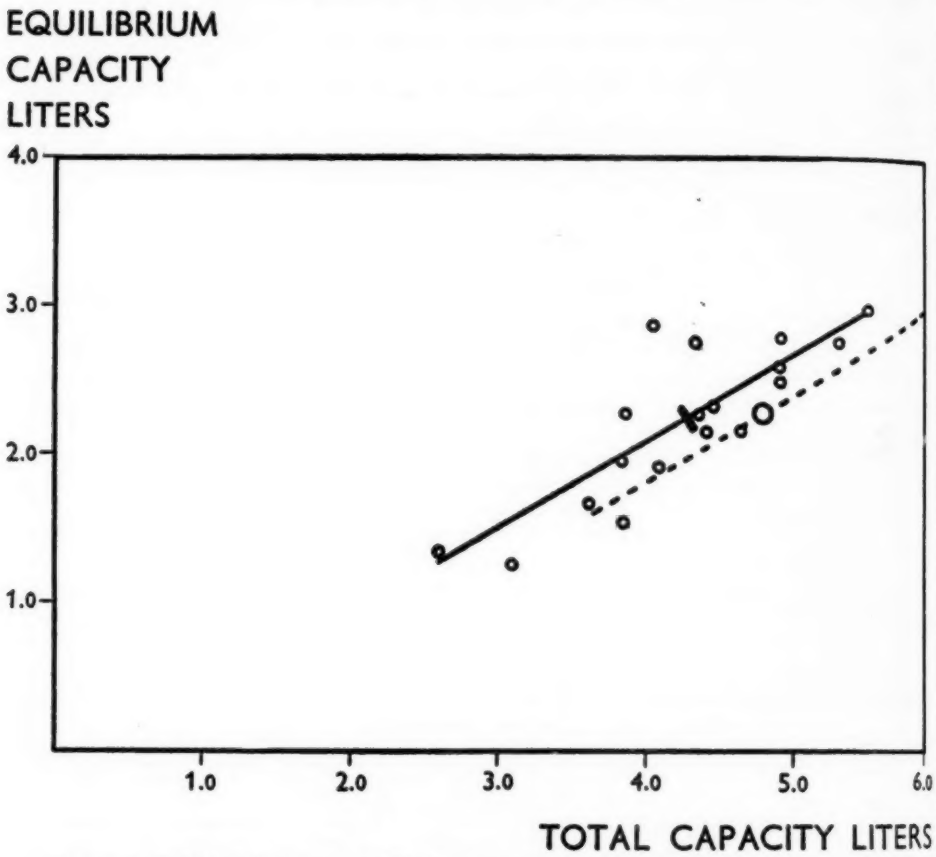

CHART 1. Relation between equilibrium capacity (mid-capacity) and total capacity (total pulmonary volume) following termination of pneumothorax in 18 women who had effusions during pneumothorax treatment.

	Regression line and mean value	Regression equation	Regression coefficient	Correlation coefficient
Normal females (not plotted)	----O----	$Y = 0.60 \times -0.65$	0.60 ± 0.12	0.78 ± 0.09
Females who had pleural effusions (0)	——+——	$Y = 0.59 \times -0.29$	0.59 ± 0.10	0.83 ± 0.07

It was found, by variance analysis, that the total capacity, as well as the vital and equilibrium capacities, showed a probably significant difference ($0.01 < P < 0.05$), while for the residual capacity the difference was only possibly significant ($0.05 < P < 0.2$).

In other respects, the material proved to be too small to permit an investigation of the effect produced by the length of the period of treatment, which may,

of course, be thought to entail variations in function after conclusion of treatment. The same applies to the significance of symptoms (pain, fever, etc.) occurring a considerable time before thoracocentesis and the induction of pneumothorax, the occurrence of larger amounts of fibrin in connection with the initial thoracoscopy, the degree of the initial collapse, due to adhesions,etc.

If we now turn to the values of the respiratory dead-space, we find that these generally showed somewhat higher values than can be considered completely normal, indicating an impaired ventilatory economy. The values are too few in number to permit a statistical analysis with men and women separately or in any subgroups, but the general tendency to an increase of both the absolute and the relative values (in relation to the tidal volume) seems nevertheless clear. (Compare with the normal values mentioned above.)

DISCUSSION

What, then, is the importance of these results of studies on patients who were treated with pneumothorax for pleurisy with effusion? The cause of the diminished vital and total capacity is clear. It is perfectly natural that the adhesions between the pleural surfaces which usually follow this treatment should cause a reduction of these two capacities, which require full freedom of movement for the lung if they are to attain their maxima. At the same time, it may be observed that, in spite of relatively slight roentgenological pleural changes and with usually inconspicuous retraction, the lung capacities investigated were evidently affected, probably chiefly due to the impaired motion of the diaphragm, but also on account of some reduction of thoracic mobility caused by adhesions between the pleural surfaces.

It is of great interest that equilibrium and residual capacities increased in their relation to the total capacity, and that their absolute values changed less. The hypothesis already mentioned seems to supply a satisfactory explanation for the increase in the relative values. It also facilitates the understanding of the cases investigated.

One must assume that in cases with pleural symphysis and especially with diaphragmatic adhesions to the thoracic wall relatively large parts of the lungs are not as effectively ventilated as the rest of the lung. These parts or "pockets" of the lung are functionally inferior on account of hypoventilation. Conditions exist for a similar increase of the relation of the equilibrium capacity and residual air and the total capacity, as that which has been shown to develop with intrapulmonary changes. As this investigation has shown, such a change in the values under discussion actually does arise and this provides valuable support for the correctness of the hypothesis.

The cause of the rise in the dead-space value that has been demonstrated must be the same as that of the increased relative lung-volume values; namely, the reduced ventilation in certain parts of the lung. For it was proved empirically (for example in bronchostenosis) that a delaying of the gas mixing in the lung by uneven ventilation has the same effect on the dead-space value as an enlarged dead-space. This was proved also theoretically by the author (11).

Otherwise, this absolute and relative increase of the dead-space value occurs most commonly in cases with real enlargement of the respiratory dead-space in emphysema. There is, in general, no direct reason for suspecting emphysema in the cases of pleurisy investigated here; but one of the highest values (in case 25) can, nevertheless, be explained in this way, since between the ages of 8 and 20 the patient had suffered from typical bronchial asthma. In the other cases with particularly high values (cases 22 and 26) this cause is absent, but in the first of these there is according to the roentgenogram, probably following strumectomy in 1938, a tracheal stenosis that has given rise to a distention of the lung and, in this way, to the increased dead-space value.

In cases in which pleural symphysis has arisen following pneumothorax treatment, this must have its share in the impairment of function that appears with a heightening of the relative lung-volume values also when infiltrative or indurative intrapulmonary processes act in the same direction. The methods employed do not, however, permit distinguishing between the effects of the two factors. In the single case it may be very difficult, without the support of roentgenograms and other clinical facts, to decide whether the essential cause of the impairment of function is, emphysema, intrapulmonary fibrosis or hypoventilation of a relatively normal parenchyma, caused by reduced mobility of thorax and diaphragm.

To some extent radiography affords a certain guidance in this connection. In cases without parenchymal changes, the roentgenologically visible pleural changes are rather slight; in agreement with this, only minor changes in the relative lung-volume values have occurred. It is different in cases with parenchymal lesions. As is evident from the case reports, the majority of cases had considerable or severe dyspnea and, in agreement herewith, marked increases are found in the values of the relative lung volumina. As example, see case 5 in table 1. The X-ray picture (figure 1) shows unexpandable lungs with bilateral adhesions between the diaphragm and the thoracic wall, and encapsulated effusions. In the parenchyma of the upper lobes contracting lesions are present, but the lower lobes appear relatively normal. It is, therefore, probable that the

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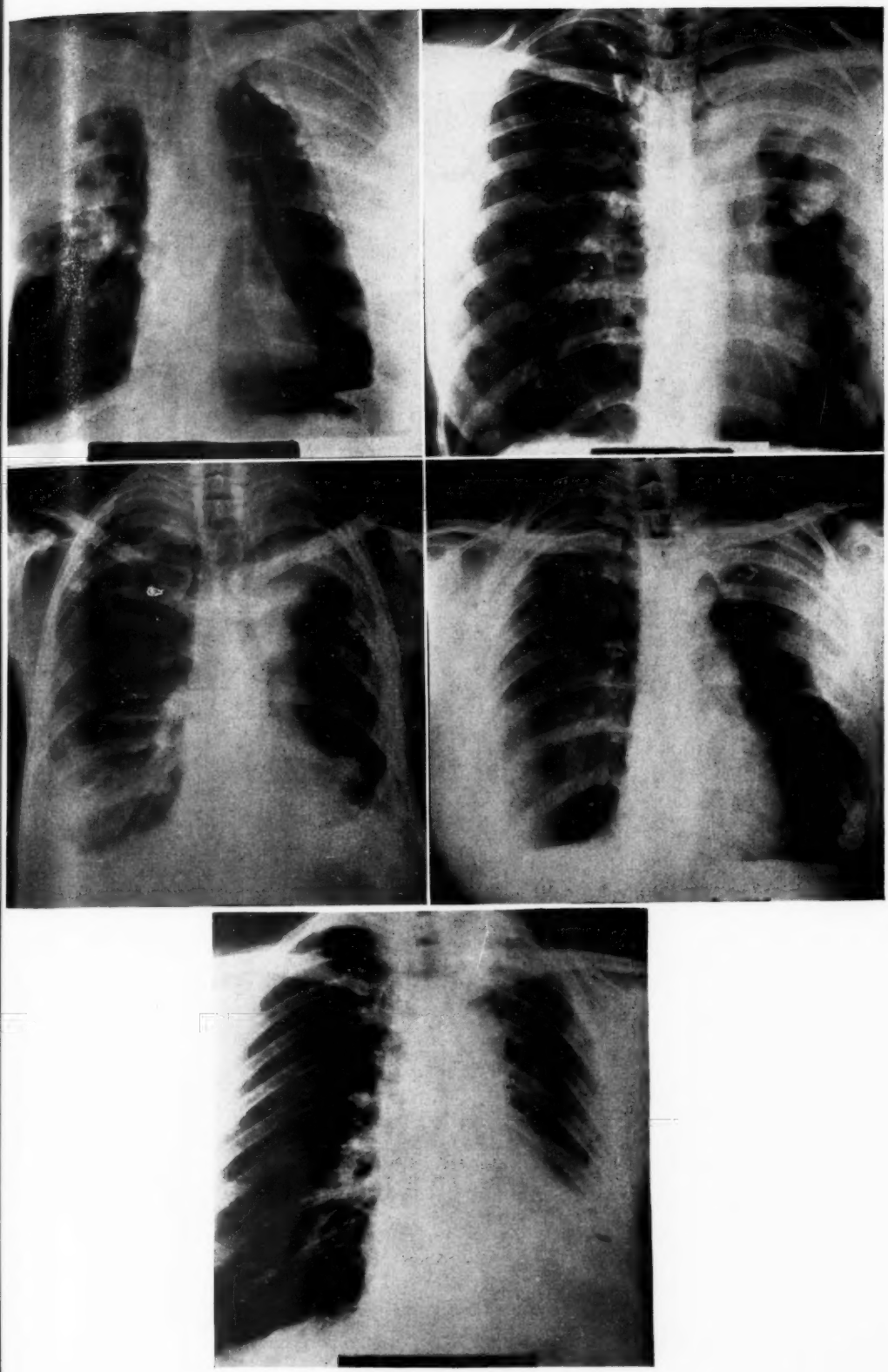
FIG. 1. (Case 5.) (Upper left.) Marked ventilatory insufficiency, pleurally conditioned. Chronic phthisis on the right side with cavitation, 2 to 3 cm. in diameter. Apical fibrous phthisis on the left side. Considerable pleural effusions in layers, 4 to 5 cm. in width on both sides (unexpandable lungs) after pneumothrax with effusions during reëxpansion. Dyspnea ++.

FIG. 2. (Case 8.) (Upper right.) Contraction of the right upper lobe owing to bronchostenosis and distention of the middle and lower lobes. Thickening of the pleura and retraction of the left lung after pneumothorax with effusion during reëxpansion. Dyspnea ++.

FIG. 3. (Case 11.) (Centre left.) Ventilatory insufficiency of pleural origin. Contracting phthisis in the right apex with small cavities. Obliteration of the costophrenic sulci with elevation of the diaphragm laterally on both sides after bilateral pneumothorax with effusion on the left side. Dyspnea +++.

FIG. 4. (Case 9.) (Centre right.) Compensatory emphysema and marked ventilatory insufficiency after bilateral pneumothorax and oleothorax treatment, causing retraction of the lungs and reduced mobility of the diaphragm. Dyspnea ++.

FIG. 5. (Case 4.) (Lower.) Basal retraction of the left lung after pneumothorax treatment. Only slight functional impairment. No dyspnea.



ventilatory insufficiency is largely caused by the pleural changes. Both the low total capacity and the increased relative lung-volume values would indicate this.

In another case (no. 8, table 1), dyspnea also arose, for which the roentgenogram afforded a fairly adequate explanation. It (figure 2) showed a considerable retraction of the left lung as a sequela to earlier pneumothorax treatment. In addition, probably due to bronchostenosis, the right upper lobe is maximally contracted and, in the main, only the right lower and middle lobes appear to have parenchyma capable of functioning. It, therefore, seems understandable that both a considerable decrease of the total capacity and an increase of the relative values have developed. Probably on account of a distention of the functioning parenchyma and hypoventilation of other parts, the dead-space value is somewhat larger than usual in women. The relative value, however, is fairly normal.

In case 11 (table 1) with a very small total capacity and with very high relative lung-volume values, parts of both lungs are shrunken and the diaphragms are elevated and adherent to the lateral chest wall, as a residue following earlier bilateral pneumothorax treatment. The extensibility of the lung is evidently much reduced, perhaps, above all, on account of adhesions between the diaphragm and the thoracic wall (figure 3). At the time of examination, the intrapulmonary changes seemed to be of only moderate functional importance; the patient's pronounced tendency to dyspnea was probably largely caused by pleural adhesions which mainly account for her ventilatory insufficiency. The patient died after an acute exacerbation, and the postmortem examination seemed to confirm this assumption. The moderate increase of the dead-space value was apparently due to the same cause.

In other cases presented in table 1 the roentgenogram affords less guidance for estimating function. Case 9 was referred to me for examination because of dyspnea and a roentgenogram (figure 4) which was not considered to explain her dyspnea. Earlier she had had pneumothorax on both sides, which was followed by oleothorax. Later on the oil had been largely aspirated or absorbed. Spirometric examinations showed that the total capacity was low and that the relative values were much increased, indicating impaired function of the lung volume measured. The dead-space value was also abnormal, especially the considerable increase of the dead-space in percentage of the tidal volume, which was 72.7. A markedly impaired pulmonary function, with the expectation of dyspnea, was thus demonstrated, in a certain contrast to the roentgenogram. On the basis of the examination, the patient received the invalid's pension for which she was applying. The cause of her impaired function was probably in part reduced ventilation of the still functioning parenchyma, caused by pulmonary contraction, and reduced mobility of the diaphragm, and in part so-called compensatory emphysema in the same lung due to marked contraction of the previously involved parts. The oxygen saturation of the arterial blood, at rest, was maintained at 92.7 per cent.

At times, the roentgenogram may show changes indicative of more seriously impaired function than that actually existing. Case 4 (figure 5) showed retrac-

tion of the left base which led to the assumption of a considerable hypoventilation. Some reduction of the total capacity was observed as a sign of this retraction, but the relative values were fairly normal and did not indicate the existence of any important hypoventilated portions of the lung. For one reason or another, the retraction which roentgenologically appears to be of considerable degree, is functionally of lesser importance. The patient was not troubled with dyspnea.

Dyspnea in patients without parenchymal lesions was slight, at times very slight, in agreement with the relatively mild pleural changes as seen on the X-ray films; only slight disturbances of pulmonary function were demonstrated in these patients. In one case (no. 35) there was a higher degree of retraction, and in this patient, dyspnea was more pronounced. In none of these cases, however, did dyspnea interfere with their capacity for work.

PRACTICAL CONSIDERATIONS

Since this investigation has shown that evident impairment of pulmonary function occurs even with relatively slight retractions, and since the retractions which occasionally appear after pneumothorax treatment of pulmonary tuberculosis interfere to a high degree with respiratory function, the question arises whether marked retractions can be avoided.

In many cases, an effusion during pneumothorax treatment may give rise to the changes under discussion. In at least some of these cases, the more extreme degrees of retraction may probably be avoided if, in the presence of a prolonged effusion, pneumothorax treatment is terminated in time. Since obliterative pleuritis often develops in these cases, which will gradually render further treatment impossible, and since the risk of empyema is relatively great in precisely these cases, the decision to replace pneumothorax treatment with some other form of collapse therapy should be facilitated. There is also reason to believe that, with extended indications for primary apical thoracoplasty, a number of troublesome complications of pneumothorax treatment may be avoided. This change in the indications for treatment should be to the advantage of pulmonary function, although at first glance the contrary might appear to be the case. Apical thoracoplasty causes a relatively slight reduction of function. Cournand and Richards (1) state the advantage from the standpoint of physical capacity of substituting a good thoracoplasty for a poor pneumothorax. In favorable cases, the greater part of the parenchyma of the inferior lobe can be spared, and if there is, above all, good diaphragmatic mobility, the operated side can manage a large part of the respiratory gas exchange. There would not appear to be much prospect of succeeding, with so-called rational treatment of exudates and continued pneumothorax, in escaping the threatening reduction of function.

A further group of cases in which there is the threat of impairment of function comprises those in which lung retraction appears without effusion. In connection with pneumothorax refills, one then finds initial pressures which more and more tend in the negative direction, and the interval between the refills may be made longer and longer without the lung being expanded. Several of the above-

described cases have been of this type. Also in such cases, therefore, other collapse therapy should eventually be considered in good time.

SUMMARY

Twenty-five patients with pleurisy with effusion without parenchymal lesions, and in whom so-called preventive pneumothorax treatment had been terminated, were examined by the author's method for the estimation of the total lung volume and its subdivisions and of the respiratory dead-space.

The following results were obtained:

1. Total and vital capacities were diminished.
2. Equilibrium and residual capacities were not generally diminished to the same degree, and their share in the total capacity was thus increased.
3. While the diminished total and vital capacities were due to the impairment of the thoracic and diaphragmatic mobility through pleural adhesions, the cause of the increased relative lung-volume values was a hypoventilation of certain parts of the lung, provoked by the same cause.

In 11 cases of terminated pneumothorax treatment chosen to throw light on the subject, and with more or less extensive parenchymal lesions, the following was found:

4. The lung function, in several cases, was seriously impaired, manifesting itself in low total and vital capacities, considerable increase of the relative lung-volume values and in certain cases increased values for the respiratory dead-space.
5. The cause of this was, in some cases, in part parenchymal contraction with so-called compensatory emphysema and reduction of the parenchyma, but in the majority of cases the cause was pleural changes following pneumothorax treatment (ventilatory insufficiency).
6. In view of the very serious impairment of function that may result when a lung retraction complicates pneumothorax treatment, it is suggested that in certain cases this treatment should be abandoned and replaced with other collapse measures.

SUMARIO

A 25 enfermos que padecían de pleuresía con derrame sin lesiones parenquimáticas y en los que había terminado el llamado neumotórax terapeútico preventivo, se les examinó con la técnica del autor para calcular el volumen pulmonar total y sus divisiones y el espacio respiratorio obliterado.

Obtuviéronse los siguientes resultados:

1. Hubo disminución de la capacidad total y la vital.
2. En general no disminuyeron en grado igual la capacidad equilibradora y la residual, de manera que aumentó la participación de las mismas en la capacidad total.
3. Aunque la disminución de la capacidad total y vital se debió a haber atenuado la movilidad torácica y diafragmática las adherencias pleurales, la causa del relativo aumento de las valores del volumen pulmonar fué una hipoventilación de ciertas partes del pulmón provocada por la misma causa.

En 11 casos de neumotórax terapeútico terminado que se escogieron para lanzar luz sobre el asunto y con lesiones parenquimáticas más o menos extensas observóse lo siguiente:

4. La función pulmonar en varios casos se afectó gravemente, traduciéndose esto por capacidades total y vital bajas y considerable aumento de los valores relativos del volumen pulmonar y en ciertos casos por aumento en la proporción del espacio respiratorio obliterado.
5. La causa de esto fué en algunos casos en parte la contracción parenquimática con el llamado enfisema compensador y reducción del parénquima, pero en la mayoría consistió en alteraciones pleurales consecutivas al neumotórax terapeútico (insuficiente ventilacion).
6. En vista de la gravísima insuficiencia functional que puede sobrevenir cuando una retracción pulmonar complica el neumotórax terapeútico, en ciertos casos convendría abandonar este tratamiento suplantándolo con otros métodos de colapso.

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STUDIES IN CHEMOTHERAPY OF TUBERCULOSIS[1,2]

VIII. The Comparative Action of Four Sulfones in Experimental Tuberculosis in Guinea Pigs and the Combined Action of Streptomycin with One of the Sulfones

M. I. SMITH, Wm. T. McCLOSKY AND E. L. JACKSON

It was shown previously (4) that streptomycin and sodium p,p′-diaminodiphenylsulfone-N,N′-didextrosesulfonate (promin) mutually potentiated each other when applied together in the treatment of guinea pigs infected with tuberculosis. It seemed probable that the synergism would hold for other sulfones as well and consequently work has been in progress in an attempt to find a sulfone less toxic and if possible more effective than promin.

The present paper is a report of such a study with three sulfones which have become available to us in sufficient quantity. These were studied for chemotherapeutic efficacy in comparison with promin. At the same time the combined effect of streptomycin with one of the sulfones was also studied. The supply of streptomycin was limited and it was not possible to study the effect of this drug alone under the same experimental conditions.

The compounds we were able to study in the present investigation were:

I. Sodium salt of 4-amino-4′-galacturonylaminodiphenylsulfone (galacturonide), prepared in the laboratories of Endo Products Co. and supplied by Dr. Samuel M. Gordon.

II. 4-Amino-4′-ureidodiphenylsulfone (carbamyl), synthesized in the laboratories of Schering Corporation and supplied by Dr. Erwin Schwenk.

III. 4-Amino-4′-n-propylaminodiphenylsulfone (n-propyl), synthesized in this laboratory by the reaction of n-propyl bromide with 4,4′-diaminodiphenylsulfone, the details of the procedure having been supplied by Dr. L. A. Sweet, Parke, Davis and Co.

IV. Sodium p,p′-diaminodiphenylsulfone-N,N′-didextrosesulfonate (promin), supplied by Parke, Davis and Co.

The streptomycin used in this study was generously supplied by Charles Pfizer and Co. and Eli Lilly and Co.

EXPERIMENTS

A series of 120 guinea pigs, weighing about 300 to 350 grams, were inoculated intraperitoneally with 0.5 mg. of a homogeneous suspension of human tubercle bacilli H37Rv[3] per cc. of sterile saline, and were divided into six equal groups of 20 as follows:

Group A: Treated with streptomycin, 10,000 units per kg. intramuscularly twice daily, 9 a.m. and 4 p.m., plus 0.15 to 0.3 g. per kg. of the galacturonide given orally once a day.

[1] From the Division of Physiology, National Institute of Health, Bethesda, Maryland.

[2] Other papers in this series are enumerated under References (1, 2, 3, 4, 5, 6, 7).

[3] The culture was furnished by Mr. Wm. Steenken, Jr., Committee on Chemotherapy of Tuberculosis, National Tuberculosis Association; Dr. Leroy U. Gardner, Trudeau Sanatorium, Chairman.

Group B: Treated with 0.15 to 0.3 g. per kg. of the galacturonide, as above, but without streptomycin.
Group C: Treated with 0.3 to 0.5 g. per kg. promin, given orally once a day. This group served as a reference standard for comparison of the efficacy of the other sulfones.
Group D: Received 0.5 g. per kg. of the carbamyl derivative orally once a day.
Group E: Received 0.5 g. per kg. of the n-propyl derivative orally once a day.
Group F: Untreated controls.

The treatment, begun the day after infection, was carried out regularly five days a week, with a double dose on the fifth day, for a period of nine weeks. Daily dosage in the first three groups was planned to be 0.3 g. per kg. for groups A and B and 0.5 g. per kg. for group C, which are equivalent when computed on the basis of diaminodiphenylsulfone content. However, it was necessary to reduce them to 0.15 and 0.3 g. per kg., respectively, for a few days at intervals on account of drug toxicity as evidenced by excessive loss of body weight. Dosage in groups D and E was uniformly maintained at 0.5 g. per kg. There was no evidence of toxicity from these latter compounds at any time.

All treatment was discontinued sixty-three days after infection. At ninety days after infection all the survivors were tuberculin tested, using 0.01 mg. PPD in 0.1 cc. salt solution intracutaneously. The reactions were recorded twenty-four and forty-eight hours after injection. At 98 to 103 days after infection all the survivors were killed with chloroform, autopsied, and the extent of tuberculous involvement noted and rated on the basis of 0 to 4 in the organs and tissues of predilection as previously described (2), with a possible maximum of 20. In cases of doubtful lesions smears were made of the suspected materials and stained with Ziehl-Neelsen stain for microscopic examination and when feasible suspensions of the material in sterile saline were inoculated into the right groin of each of 2 guinea pigs for tuberculin testing and postmortem examination after an incubation period of six weeks.

RESULTS

The virulence of the strain and magnitude of dosage used were such as to produce in the controls extensive generalized tuberculosis of the viscera (with ascites and pleural and pericardial effusions in many cases), within thirty to forty days, and death of 95 per cent of the animals within seventy-five days of the infection. The average tuberculosis index for this group was 16.3, with a range of 9 to 20, out of a possible maximum of 20.

Ninety-five per cent of the animals of group A, treated with streptomycin and the galacturonide, were in excellent condition and gaining weight at the time the experiment was terminated, about 100 days after infection, and after a period of nearly forty days without treatment. One of the animals in this group died within twenty-four hours following the intracutaneous injection of PPD; this should be regarded as a tuberculin allergy death, since this animal had been in good condition, and since many in this group (95 per cent) gave positive tuberculin reactions. Postmortem examination of the animals in this group revealed no gross evidence of tuberculosis, or doubtful and negligible

TABLE 1

Effect of treatment with streptomycin and galacturonide in guinea pigs infected with 0.5 mg. H37Rv intraperitoneally

Treatment continued sixty-three days. Killed 100 days after infection

NUMBER	WEIGHT, GRAMS		PPD	ORGANS INVOLVED	TUBERCULOSIS INDEX	SMEARS	SUBINOCULATION TESTS	
	Initial	Final					Tissue suspension	Result
1	390	604	2+	Small omental lymph node and few doubtful pin-point lesions in liver and lung	±	Negative		
2	382	672	+	None	0			
3	396	628	2+	None	0			
4	382	644	+	None	0		Spleen	Positive
5	340	616	2+	Small omental lymph node	±	Negative	Spleen and lymph node	Positive
6	394	764	+	None	0		Spleen	Positive
7	402	800	2+	None	0		Spleen and lung	Positive
8	308	696	+	None	0		Spleen and lung	Positive
9	252	580	2+	Doubtful spleen (1.6 g.)	±	Negative	Spleen	Positive
10	318	420	3+	Minimal lesions in omentum, liver, lung, and peritoneum	2			
11	334	500	Died	Minimal lesions in omentum, liver and lung	3			
12	310	520	+	Few military tubercles in lungs	1			
13	376	704	2+	None	0			
14	354	612	+	Small (5 mm.) consolidated area in upper right lobe	±	Negative	Spleen and lung	Positive
15	382	680	±	Small omental lymph node	±	Negative		
16	332	632	+	Doubtful few miliary lesions in liver and lung	1		Spleen and lung	Positive
17	326	618	+	Minimal lesions in omentum, spleen and liver	2	Negative	Spleen	Positive
18	328	628	+	None	0		Spleen	Positive
19	354	684	+	None	0		Spleen and lung	Negative
20	336	624	+	Small necrotic omental lymph node	±	Negative		

lesions in 75 per cent,[4] and only minimal lesions in the remainder. However, subinoculation of spleen or other tissue suspensions into the inguinal region of

[4] Animals with a tuberculosis index rating of 0 or ±.

normal guinea pigs resulted in positive PPD reactions and glandular involvement at the site of inoculation in all but one of the animals tested. A detailed summary of the findings in this group is given in table 1.

Table 2 and figure 1 show the results in summary form of the entire experiment. It will be seen that, at the dosage levels used, all the sulfones retarded the disease process to about the same degree as promin. The mortality rate was distinctly

TABLE 2

January 3, inoculated 0.5 mg. H37Rv intraperitoneally. Treatment begun January 4 and continued till March 8, sixty-three days. Tuberculin tested (.01 mg. PPD intracutaneously) April 5, twenty-six days after discontinuing treatment. Experiment terminated April 12 to 16, 98 to 103 days after infection

GROUP AND DRUG	A STREPTOMYCIN + GALACTURONIDE	B GALACTURONIDE	C PROMIN	D CARBAMYL	E N-PROPYL	F CONTROLS
Dosage in units or grams per kg. per day	2 × 10,000 +0.15–0.3	0.15–0.3	0.3–0.5	0.5	0.5	0
Mortality per cent at 63 days, end of treatment period	0	35	15	40	15	80
Mortality per cent at termination of experiment, 98–103 days	5	70	40	50	40	95
Number reacting to PPD in relation to survivors 90 days after infection	18/19	6/8	13/13	9/10	12/14	1/1
Number losing weight in relation to survivors at termination of experiment	0/19	1/6	3/12	5/10	4/12	1/1
Tuberculosis Index						
Range	0–3	0–13	0–18	3–11	0–15	9–20
Mean	0.6	5.9	6.2	6.2	5.8	16.3
Spleen weight, grams						
Range	0.8–2.1	0.6–11.3	0.7–13.9	1.3–5.9	1.0–8.8	0.9–9.2
Mean	1.3	2.9	3.2	2.4	2.4	5.5
Average weight gain in grams	281	41	148	161	172	17
Per cent with doubtful or no lesions	75	5	15	0	10	0
Chemotherapeutic effectiveness (ratio of extent of tuberculous involvement in controls and treated groups)	100/3.7 27.0	100/36.2 2.7	100/38.0 2.6	100/38.0 2.6	100/35.6 2.8	

higher in the galacturonide group than in the promin or the other sulfone groups, and this may be due in part to the higher toxicity and, possibly the greater cumulative action of this compound. It is significant that the animals in group A, receiving the same amount of this drug in addition to streptomycin, were not affected in the same manner.

The chemotherapeutic effectiveness of the several compounds studied, expressed as the ratio of extent of tuberculous involvement in the controls and treated groups ranged from 2.6 to 2.8 for the four sulfones and 27.0 for the group

treated with streptomycin and the galacturonide. Since there was no group in this series receiving streptomycin alone it is not possible to appraise accurately

A. STREPTOMYCIN + NH_2⬡SO_2⬡NH–C(H)(O)–$(CHOH)_3$ CHCOONa

B. NH_2⬡SO_2⬡NH–C(H)(O)–$(CHOH)_3$CHCOONa

C. $OHCH_2(CHOH)_4$ CHNH(SO_3Na)⬡SO_2⬡NHCH(SO_3Na) $(CHOH)_4$ CH_2OH

D. NH_2⬡SO_2⬡$NH \cdot CONH_2$

E. NH_2⬡SO_2⬡$NHCH_2CH_2CH_3$

F. CONTROLS

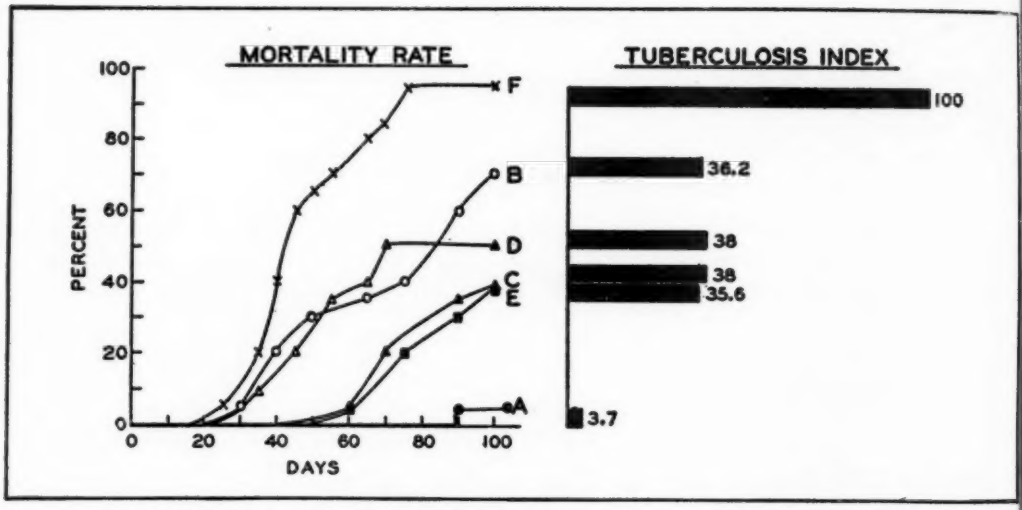

FIG. 1. Mortality rate and tuberculosis index of five groups of treated animals in comparison with untreated controls (group F).

A. Treated with streptomycin intramuscularly and galacturonide orally.

B. Treated with galacturonide orally.

C. Treated with promin orally.

D. Treated with carbamyl derivative orally.

E. Treated with n-propyl derivative orally.

Treatment was begun day after infection and continued for sixty-three days. Experiment terminated 98 to 103 days after infection, all survivors killed.

the full value of the combined treatment, but in the light of other experiences in this laboratory it is not believed that the effect obtained in group A could have been achieved with the antibiotic alone.

DISCUSSION

The present experiments undertaken with a view of testing several new sulfones in the hope of finding a safer and if possible a more effective compound than promin for application in the combined treatment with streptomycin have borne only partially fruitful results. On the basis of preliminary pharmacological studies with the monogalacturonyl derivative of diaminodiphenylsulfone in rats it appeared to offer advantages over promin because of its lower acute toxicity on intravenous injection, longer retention in the body, and a more favorable distribution in the tissues as between the liver and blood. However, on continued oral administration to guinea pigs, the procedure employed in the present chemotherapeutic tests, this compound actually proved to be more toxic than promin, probably by virtue of its better absorption, longer retention and greater cumulative effects. Nevertheless, the combined treatment with this compound and streptomycin resulted in a degree of protection against the disease in the experimental animals at least as great as from the application of streptomycin and promin in the previous study (4). Actually the results in the present study appear to indicate a higher degree of efficacy, since treatment was continued for only sixty-three days, and the animals were examined for evidence of tuberculosis after a six weeks' period of no treatment, whereas in the previous study treatment was continued with relatively smaller doses of streptomycin without interruption to the end of the experiment. Moreover, the infection in the present study was considerably more virulent as evidenced by 95 per cent mortality in the controls within seventy-five days as against 65 per cent mortality at 10 1days in the previous study.

The nearly uniformly positive response to tuberculin of the animals in group A, despite the low incidence of gross tuberculous infection and the minimal lesions found in the few, suggests that the allergy induced by the initial infection has not abated in the course of treatment, and perhaps also indicates that these animals may have acquired and have retained some degree of immunity. It would be interesting to study the response of such animals to reinfection with a standard dose of bacilli of standard virulence. That these animals were not sterilized by the treatment is evident from the fact that the subinoculation tests gave almost uniformly positive results.

The search for a better sulfone than promin has not been wholly fruitless. The n-propyl derivative of diaminodiphenylsulfone, used in group E, though no more effective than promin in reducing the extent of tuberculous involvement, as indicated from present and previous experiments (8, 9) is definitely less toxic than promin, this probably by virtue of its poor solubility and absorbability.

Because of its insolubility and low toxicity it has been impossible to obtain an LD_{50} dose of the n-propyl derivative. A test on the comparative subacute and chronic toxicity of this compound and promin was carried out on guinea pigs. The compounds were administered in 1.0 g. per kg. doses twice daily to two groups of animals 10 each over a period of fifteen days. All the animals receiving promin developed cyanosis, hyperexcitability, tremors and flaccid

paralyses and died in three to five days. Reduction of hemoglobin and the appearance of methemoglobinemia were noted in all cases. The animals receiving the n-propyl compound showed no symptoms, no blood dyscrasias and gained weight normally. Blood level determinations made at various intervals from three to twenty hours following the last dose during the course of treatment showed a range of 40 to 85 mg. per cent in the promin animals and 3.4 to 4.8 mg. per cent in the n-propyl group. It may be concluded from this that the n-propyl derivative is less than one-fifth as toxic as promin and, while it is difficult to attain high blood levels with this drug, they seem to be sufficiently effective judging from the chemotherapeutic response. It seems quite clear, therefore, as previously pointed out (6), that mono-substituted alkyl derivatives of diaminodiphenylsulfone have an advantage over the mono- and di-substituted water-soluble derivatives by being equally or possibly more effective, less toxic and better retained in the body, even though their absorbability is poorer.

SUMMARY AND CONCLUSIONS

1. The chemotherapeutic efficacy of three mono-substituted derivatives of diaminodiphenylsulfone has been studied in experimental guinea pig tuberculosis in comparison with promin. The compounds were the monogalacturonyl derivative (I), the monocarbamyl derivative (II) and the mono-n-propyl derivative (III). The chemotherapeutic effectiveness of these compounds, expressed as the ratio between the extent of tuberculous involvement in the controls and treated animals was 2.7 for I, 2.6 for II and 2.8 for III, as compared with 2.6 for promin. The n-propyl derivative is less than one-fifth as toxic as promin.

2. The chemotherapeutic effectiveness in a group of animals treated with streptomycin and compound I was 27.0. Seventy-five per cent of the animals in this group showed no gross evidence of tuberculosis or only doubtful and insignificant lesions, though 95 per cent of them reacted to intracutaneous tuberculin, and subinoculation tests with tissue suspensions gave positive results in nearly all cases.

3. The combined application of streptomycin and the monogalacturonyl derivative of 4,4′diaminodiphenylsulfone in the treatment of experimental tuberculosis gave as good results as those previously reported with streptomycin and promin.

SUMARIO Y CONCLUSIONES

1. En la tuberculosis experimental del cobayo estudióse la eficacia quimioterapéutica de tres derivados monosustitutivos de la diaminodefenilsulfona, comparándola con la de la promina. Trátase de los derivados monogalacturonílico (I), monocarbamílico (II) y mono-n-propílico. Expresada en forma de proporción entre la extensión de la invasión tuberculosa en los testigos y en los animales tratados, la eficacia quimioterapéutica de dichos compuestos representó 2.7 para el I, 2.6 para el II y 2.8 para el III, comparado con 2.6 para la promina. El derivado n-propílico resultó ser más de cinco veces menos tóxico que la promina.

2. En un grupo de animales tratados con estreptomicina y el compuesto I la eficacia terapéutica llegó a 27.0. Setenta y cinco por ciento de los animales de este grupo no revelaron signos macroscópicos de tuberculina administrada por vía subcutánea, y las pruebas de subinoculación verificadas con suspensiones de tejidos resultaron positivas en casi todos los casos.

3. La aplicación combinada de la estreptomicina y el derivado monogalacturonílico de la 4,4′-diaminodifenilsulfona dió en la tuberculosis experimental tan buenos resultados como los comunicados previamente con la estreptomicina y la promina.

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DIAGNOSTIC CULTURE OF TUBERCLE BACILLI

A Simplified Procedure in Public Health Work

MARJORIE VAN VRANKEN[1]

Within the past few decades, diagnostic culture methods for determining the presence of mammalian tubercle bacilli in pathological materials have superseded animal inoculations which were preferred in diagnostic laboratories prior to this (1). Laborious and persistent trials of culture methods have led to the conviction that this important feature of the specific triad of tuberculosis diagnosis (2) should now be available universally in all public health laboratories and that simplicity and accuracy should be the criteria of the technique used in its performance (3). It is with this in mind that the following report is presented in the hope that it will not only aid others in the performance of the test but that it will stimulate a more wide-spread use of this most valuable specific diagnostic aid in tuberculosis among those interested in the extension of public health facilities for this disease and in the ultimate welfare of the tuberculous patient.

In a routine testing for the presence of tubercle bacilli in a large number of sputum, urine and gastric specimens received in the Colorado Public Health Laboratories from various parts of the State, the method of procedure was to examine the specimens or concentrates from them by direct smear and Ziehl-Neelsen staining methods and, in addition, to perform an oxalic acid treatment (4) with Petragnani's medium and the Corper egg-yolk culture medium (5). Thus, 3,948 culture tests were performed from January, 1944 to December, 1945, with the result that 179 positive cultures were found which had been negative on direct smear. Of these 179, 5 became positive after an interval somewhere between six weeks' and six months' incubation at 37° C. The majority, 174, proved positive within a six weeks' incubation period. Unfortunately, the media used were not recorded in this series. These figures leave no doubt of the value of the culture method for disclosing tubercle bacilli in public health work.

In order to determine the comparative value of the two media, Petragnani's multiple mixture (3) and Corper's simple egg-yolk medium, the cultural findings were segregated on this basis since December, 1945, with the following results recorded in table 1.

It is noted from the findings recorded in table 1 that the positive cultures obtained with the use of an equal volume of 5 per cent oxalic acid at 37° C. for thirty minutes for destroying contaminants and planting on the egg-yolk medium (Corper) exceeded the positives on Petragnani's medium in a routine diagnostic culture test, 74 to 33. Both methods disagreed to some extent with each other in that a total of 87 positive results were obtained on either one or the other culture medium. The significance of this could be exaggerated if it were not known that routine clinical specimens may run irregularly at times so far as the distribution of small numbers of tubercle bacilli are concerned. The lack

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of homogeneity in clinical specimens so far as tubercle bacilli are concerned accounts also for the fact that the more tubes planted, the more positive cultures may accrue regardless of the medium used as a nutrient, provided the nutrient falls into the category of one of those efficiently supporting growth from small plantings. However, regardless of this, the findings with the egg medium are strikingly more favorable, which may possibly be explained by the better nutrient properties of the egg-yolk as compared with the Petragnani medium hampered by a retardant dye, malachite green, and multiple ingredients serving only as diluents for the good nutrient—the egg-yolk.

In the search for a more suitable reagent than sodium hydroxide, or one that would be adaptable to elaboration with the oxalic acid reagent, Corper and Stoner (6) studied trisodium phosphate, a crystalline, chemically pure and stable alkaline salt, for its effect upon mammalian tubercle bacilli. It was found that

TABLE 1

A comparison of cultures for tubercle bacilli in sputa using Petragnani's medium and the egg-yolk medium (Corper)*

SPUTA TESTED AND TOTAL POSITIVES	PETRAGNANI'S MEDIUM			EGG-YOLK MEDIUM			POSITIVE WITH BOTH MEDIA		
	Positive at 3 weeks	Positive at 6 weeks	Positive after 6 weeks	Positive at 3 weeks	Positive at 6 weeks	Positive after 6 weeks	Positive at 3 weeks	Positive at 6 weeks	Positive after 6 weeks
784 specimens yielded a total of 87 positives†	19	12	2	32	34	8	11	7	2
	Total 33			Total 74			Total 20		

* The oxalic acid preliminary treatment was used for all these sputa with neutralization with sodium hydroxide before planting.

† At least 3 tubes of culture medium were planted from each sputum on each medium used. Forty-two of the 87 positive cultures were negative by direct smear examination.

this reagent possessed a number of decided advantages for destroying contaminations in sputum, urine, gastric contents and pus in preparation for the cultivation of tubercle bacilli in clinical-pathological and public health work. The advantages were that a 23 per cent sodium phosphate ($Na_3PO_4 \cdot 12H_2O$) solution in equal volume added to these specimens could remain in contact at room temperature for up to seven days without harm to the tubercle bacilli, and this amount and time sufficed in most cases to destroy all contaminants found in the usual pathological specimen. This enables the technician to prepare his material without rush and allows sufficient time to prevent the usual cautious watch period necessitated by all reagents previously described where neutralization had to be performed within one-half to two hours at least, frequently breaking up the day's continuity in laboratory work and necessitating continuous handling to consummation of the planting. In addition, if an oxalic acid preparation were forgotten and allowed to exceed the two-hour contact period without neutralization, the specimen, of which usually only one is available in

public health work, was lost; while in the sodium phosphate procedure, a day or two additional contact was not particularly detrimental to the tubercle bacilli. With a view, therefore, to comparing the new sodium phosphate procedure with the tried and reliable oxalic acid procedure previously chosen, the two reagents were tested on a consecutive series of 1,000 specimens (mostly sputa) received in the Colorado Department of Health Laboratories. All determinations for growth of tubercle bacilli were tested on the glycerol egg-yolk medium (Corper), which in our hands has proved to be the best nutrient for mammalian tubercle bacilli thus far described. The results of these tests are recorded in table 2.

Although the figures recorded in table 2 are not exactly comparable because the 1,000 consecutive specimens were tested at different times by the two preliminary treatment methods, it is obvious that the trisodium phosphate method appears to yield a better percentage of positive cultures, 127 as compared with 108 per 1,000 specimens examined. Its value is significantly enhanced in the "positive culture-negative direct smear group" in which case twice as many

TABLE 2

Comparison of tubercle bacillus cultures on egg-yolk medium following the treatment of 1,000 specimens either with the sodium phosphate or the oxalic acid

METHOD OF TREATMENT	POSITIVE BY DIRECT SMEAR	CULTURES POSITIVE	POSITIVE CULTURE FROM DIRECT SMEAR NEGATIVE SPECIMENS	NEGATIVE CULTURES FROM DIRECT SMEAR POSITIVE SPECIMENS	CONTAMINATED OR LOST SPECIMENS
Oxalic acid	116	108	32	42	8
Sodium phosphate	113	127	64	35	13

positive results were obtained by the phosphate method used on routine single specimens.

In another analysis of the findings with routine health department specimens, the entire figures for the oxalic acid treated specimens were compared with those obtained when the phosphate treatment had been used to note the advantages in smear-negative specimens particularly. The oxalic acid treatment had been used from January, 1944 through December, 1945, on 3,948 specimens with the result that 179 positive cultures for tubercle bacilli were found in the absence of positive findings for acid-fast bacilli in the smears microscopically examined. From January, 1946 to September, 1946, 1,137 specimens were tested, using the phosphate treatment and planted on the egg-yolk medium with the result that 56 yielded positive cultures for tubercle bacilli in the absence of acid-fast bacilli in the smears examined microscopically. The relative findings for the same number were 179 for oxalic acid as compared with 194 for the phosphate. It is obvious that the trisodium phosphate reagent, an equal volume of 23 per cent ($Na_3PO_4 \cdot 12H_2O$) added to sputum or similar specimens is a reliable reagent for destroying contaminants usually present in such specimens without acting detrimentally upon tubercle bacilli contained in those specimens. It is even

possible to consider placing the phosphate in the specimen bottle used for collecting and shipping the specimen, even though this has not been tried by us as yet, because at room temperature the trisodium phosphate in concentration used is without detrimental effect on the viable tubercle bacilli at room temperature for up to one week's contact. It can act as a retardant to the growth of contaminants in the specimen from the time of collection until delivered to the laboratory when a day of incubation at 37° C. will destroy the remaining viable contaminating microörganisms.

SUMMARY AND CONCLUSIONS

1. As a result of a test with routine specimens, it was found that the oxalic acid egg-yolk method devised by Corper and his colleagues for the diagnostic culture of tubercle bacilli from human pathological specimens (including sputum, urine, gastric washings, purulent fluids, etc.) is superior to the treatment with the oxalic acid reagent and culture on Petragnani's malachite green multiple mixture medium used in many health and sanatorium laboratories.

2. Trisodium phosphate ($Na_3PO_4 \cdot 12H_2O$), used in equal volume of 23 per cent solution for twenty-four hours at 37° C., and studied and introduced originally by Corper and Stoner, has been found to be a superior reagent for destroying contaminating microörganisms in pathological specimens for the cultural diagnosis of tuberculosis. Combining the phosphate treatment with the egg-yolk medium (Corper) provides a simple diagnostic procedure to isolate human and bovine tubercle bacilli from routine specimens. It is recommended on the basis of extensive routine tests in public health work reported on here.

SUMARIO Y CONCLUSIONES

1. Como resultado de una prueba verificada con ejemplares corrientes se observó que la técnica de la yema de huevo y ácido oxálico, introducida por Corper y colegas, para el cultivo diagnóstico de bacilos tuberculosos procedentes de ejmplares patológicos humanos (incluso esputo, orina, lavados gástricos, líquidos purulentos, etc.) es superior al tratamiento con el reactivo de ácido oxálico y al cultivo en el medio múltiple de Petragnani a base de verde de malaquita que utilizan en muchos laboratorios de higiene y sanatorios.

2. Utilizado en un volumen igual de solución al 23% durante 24 horas a 37°C., el fosfato trisódico ($Na_3PO_4 \cdot 12H_2O$), estudiado e introducido primitivamente por Corper y Stoner, ha resultado superior como reactivo para destruir los microbios contaminantes en los ejemplares patológicos recibidos para el diagnóstico cultural de la tuberculosis. La combinación del tratamiento con fosfato con el medio de yema de huevo (Corper) ofrece un sencillo procedimiento diagnóstico para aislar los bacilos tuberculosos humanos y bovinos de los ejemplares corrientes, y recomiéndase para empleo a base de las muchas pruebas sistemáticas en obras sanitarias aquí descritas.

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REHABILITATION DIFFICULTIES[1]

EZRA BRIDGE[2]

Rehabilitation is never easy, never finished, never perfect. Its problems have been with us always.

As physicians we feel the pressure of its presence and the responsibilities it lays upon us. We must see that nothing develops that will lessen the patient's physical health; we must know the significance of different personality traits; we must be familiar with mental mechanisms and motives. We must increase our ability to influence people and remain friends.

The aim of rehabilitation is to bring about the optimum adjustment of each patient in spite of the physical defects, mental deficiencies, emotional weaknesses and social shortcomings that he may have.

All this is most worthy, but its accomplishment is most difficult. Take, for instance, the story of our own development. To obtain a contented adjustment for ourselves, our parents spend a gigantic amount of time and energy training us when we are in swaddling clothes; our teachers grow prematurely gray trying to instill into our hearts and minds valuable concepts of those social practices that keep us out of the clutches of the law; next our sweethearts, mothers-in-law and children take over; and finally each one of us devotes hours, days and years to personal improvement. The result of these diverse and well meaning attempts is only rarely satisfactory. What is usually accomplished is well stated in these words: "Outwardly I appear well adjusted, but inwardly I still have my ups and downs."

The nature of man's inner self, his psychosomatic side, is one of the complicating factors. Psychosomatic medicine means giving careful consideration to the entire man, not only to his physical problems, but also to those in the intellectual, mental and spiritual spheres. In this it resembles rehabilitation. Much is heard about it these days; it is frequent in the literature, often thought of at the bedside and constantly whispered about in consultations.

This word "psychosomatic" comes from two Greek words, Psyche and Soma; words far apart in their origin. Psyche in Greek means butterfly and also soul. Soma, or body, recalls a savage, heady liquor. Little wonder that they make trouble for the rehabilitator with his aim of contented adjustment.

Putting these two influences side by side and expecting them to exist peacefully is asking for trouble. In some natures Psyche is the dominating influence, in others Soma; in all the battle between soul and body goes on.

Take for instance George and his problem of adjustment to society. He came to us six years ago. He was a laborer. Social investigation showed he drank, hung around saloons and dives, begged from acquaintances as well as

[1] Presented at the Mississippi Valley Tuberculosis Conference, Chicago, Illinois, October 9, 1945.

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strangers. He contracted tuberculosis. We admitted him four times; he absconded an equal number. The fifth time he went AWOL, got drunk, landed in jail and finally returned to the hospital. To stop his craving for alcohol, we suggested investigating Alcoholics Anonymous. On being told what it was, he replied that drunk or sober he didn't care about being anonymous, that he was no shrinking violet. In due time we started rehabilitation.

We put him through psychological tests, made his psychograph, analyzed his personality, delved into his earlier education, inquired into his esoteric nature, searched for his latent capacities and determined his vocational proclivities. We found he was capable of no special skills and that his rehabilitation depended upon his losing his taste for alcohol. Finally we put him to work for a few hours a day as janitor's helper; came pay-day and $12 was his. Promptly he disappeared only to return in a disheveled condition three days later. Asked what happened, he replied, "Doc, I just can't stand prosperity."

Our educational efforts have so far brought a partial adjustment. George has learned something of the problem of taking care of his health. He is more cognizant of good social usage, but cancellation of his court committment is not yet feasible. His Psyche and Soma are living more peacefully together. But there is more work to be done. He must be interested in broader pursuits and stimulated intellectually. If he is let out now he will probably seek his old haunts. As long as the desire for alcohol remains he is not completely rehabilitated.

Another difficulty in rehabilitation arises from the bisexual character of our natures. Each man has non-genital characteristics belonging to woman and no woman is entirely free from certain male markings and thought patterns. This mixture has been called the mosaic of androgyny (andro-male; gynic-female). The term does not imply a lack of the primary sexual function, but complicates life for the individual by influencing his emotional, physical and social reactions.

Take the problem in emotional adjustment in Elizabeth, whom we have known since 1941. As part of the admission technique, her atavistic, parental, educational and religious backgrounds were studied. Tests by psychologists, teachers, vocational director and physicians added data. She had a sheltered girlhood. Early in life she married a man who lavished care and attention on her. Then one day he dropped dead.

After his sudden death she became a different person. Her male personality traits came to the front. Wherein before she was quietly receptive, now she was domineering, managing, tyrannical; instead of handling home affairs she walked the streets and promptly got herself into trouble. It was at this time she was found to have tuberculosis. Examination disclosed a strong, sturdy woman with shoulders broader and hips narrower than expected. Her extremities have masculine contours and her hair distribution resembles that of a male. As she improved physically a rehabilitation program was started. But to make any plan appeal to her for long was impossible. Her restlessness continued unabated. On one occasion she spirited two weak-minded women away from the hospital. Police located them in a cheap rooming house in an unimproved part of town.

But this was not allowed to discourage us. The ramifications of her health problem and her emotional and social responsibilities were again explained to her. New approaches were tried, but so far to no avail. She remains an uncontented soul, full of contradictory attitudes and actions. She illustrates well the slogan: "If the learner has not learned, the teacher has not taught."

The third case shows the difficulty in making a medical school graduate conscious of some of his problems.

John was an interne when he developed tuberculosis. His scholastic record had always been high. At the hospital he was dependable, quick to accomplish the daily tasks, pleasant with patients and associates. While under treatment with us all phases of his problems were discussed with him and, when well on the road to recovery, he was allowed to attend staff conferences where he heard repeated admonitions to patients being discharged. Finally he was given an arrested classification and a maximum sanatorium benefit discharge. He returned to part-time hospital work with our blessing.

It was not long before he was forgetting what he had been told about his health hazard. He stayed overtime on the wards, met all emergencies and accepted new responsibilities. Repeatedly we cautioned him to observe more rest and to take it easy. But, no! Now he is back in bed with an open lesion, another case to be chalked against the teacher because the learner did not learn. This propensity not to hear or appreciate what the other fellow says, is deep seated.

However, in spite of the many difficulities, rehabilitation is a beneficent development in our sanatoria. It puts new life into the staff; leads to a broader outlook; makes everyone brush up on principles and brings an inner glow to all identified with the work. The patients have more to live for and are encouraged by the renewed attention to their welfare.

But the difficulties besetting the way of the rehabilitator make the successful termination of many cases a long drawn out process.

MORTALITY STATISTICS FOR 1945

Fewer deaths occurred in the United States in 1945 than in either of the two preceding war years, according to figures released to-day by the U. S. Public Health Service. A total of 1,401,719 deaths were reported in the United States in 1945, as compared with 1,411,338 in 1944, 1,459,544 in 1943 and 1,385,187 in 1942.

In the first ten months of 1946 there were an estimated 1,162,000 deaths in the United States, as compared with 1,144,273 in the first ten months of 1945. All figures are for the continental United States and exclude deaths among the armed forces overseas.

Deaths from the major infectious diseases declined to new lows in 1945. The year set a record low for pneumonia and influenza. The total of 68,386 deaths from these respiratory causes was 8.2 per cent less than the previous minimum of 74,532 deaths in 1942 and 16.4 per cent less than the number reported for 1944.

Tuberculosis continued its decline in 1945. There were 52,916 deaths from this cause in the United States in 1945, 3.3 per cent less than the number in 1944 and fewer than in any previous year.

The ten leading causes of death in the United States are listed in table 1.

TABLE 1

Ten leading causes of death: United States, 1944 and 1945

CAUSE OF DEATH	NUMBER OF DEATHS		PER CENT OF ALL CAUSES	
	1945	1944	1945	1944
All causes	1,401,719	1,411,338	100.00	100.00
1. Diseases of the heart	424,328	418,062	30.3	29.6
2. Cancer and other malignant tumors	177,464	171,171	12.7	12.1
3. Intracranial lesions of vascular origin	129,144	124,250	9.2	8.8
4. Nephritis	88,078	91,687	6.3	6.5
5. Pneumonia (all forms) and influenza	68,386	81,804	4.9	5.8
6. Accidents excluding motor-vehicle accidents	67,842	70,955	4.8	5.0
7. Tuberculosis (all forms)	52,916	54,731	3.8	3.9
8. Diabetes mellitus	35,160	34,948	2.5	2.5
9. Premature birth	31,614	33,120	2.3	2.3
10. Motor-vehicle accidents	28,076	24,282	2.0	1.7

[From a press release of the United States
Public Health Service, dated December 27, 1946]

AMERICAN TRUDEAU SOCIETY

Postgraduate Course in Thoracic Diseases

University of Colorado Medical School, Denver, Colorado

July 28 to August 9, 1947

A Postgraduate Course in Thoracic Diseases will be given at the University of Colorado Medical School from July 28 through August 9, 1947. Dr. H. Dumont Clark says: "The first week will be devoted to anatomy, surgical anatomy, physiology, pathological physiology, anesthesia, and certain treatment techniques including oxygen therapy, aerosol therapy, and lung immobilization. Much of this work will be in the form of demonstrations in the laboratories of the University of Colorado Medical School. Various operative procedures are to be demonstrated on the cadaver. Remainder of the first week and all of the second week are to be devoted to a consideration of various thoracic diseases with emphasis on tuberculosis. Contributions of psychiatry and rehabilitation programs to tuberculosis control will be included. The pathological lesions of the various thoracic diseases will be obtained from the extensive collection at Fitzsimons General Hospital and will be shown by a new micro-projector recently obtained by the University of Colorado Medical School. . . . It may be possible for us to house the students in one of the medical fraternity buildings near the school. Reservations will be made at nearby mountain resorts so that families of students and instructors can stay there if desired."

Tuition for this two-week course will be $100.00. While it is planned primarily for physicians resident in the states of: Colorado, North Dakota, South Dakota, Nebraska, Kansas, New Mexico, Arizona, Utah, Wyoming, and Montana, undoubtedly some of those applying from other states will be accepted.

THE ISOLATION AND IDENTIFICATION OF PATHOGENIC FUNGI FROM SPUTUM
II

By

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From the New York State Hospital for Incipient Pulmonary Tuberculosis,
Ray Brook, New York

FOREWORD

This brochure represents an amplification of a similar one published in the REVIEW nearly five years ago dealing with the identification of pathogenic fungi encountered in the sputum.* The text has been revised and there is a larger number of illustrations. Particularly worthy of mention are the illustrations demonstrating the microörganisms in the stained microscopical preparations of the lung.

It is hoped that the changes in the text and the aditional illustrations will be of further aid to the laboratory worker in the rather difficult task which confronts him in identifying the offending fungus.

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*Am. Rev. Tuberc., 1942, *46*, 365.

The pathogenic fungi found in the sputum are complex in nature and present marked differences in appearance and cultural characteristics. The information required for the identification of the fungus is best acquired by means of illustrations. In the present article the text has been purposely much abbreviated and the emphasis placed on the illustrations.

It is hoped that it will serve as a useful guide to the laboratory worker interested in this type of study.

COLLECTION OF THE SPUTUM

The details concerned in the collection of the sputum are of first importance and in not a few instances that have come to our attention the identification of the fungus has rested on this factor alone. The physician or some qualified person should attend to these details. The sputum should be collected shortly after the patient awakens in the morning. A morning specimen represents the pulmonary secretions accumulated during the night and, in general, is the most satisfactory one for the examination; it is also free from food particles. Before the specimen is obtained the patient is instructed to brush the teeth and to rinse and gargle the mouth and throat. Great care must be exercised to see that the sputum comes from the lungs. Avoid all specimens of saliva or nasopharyngeal secretions. Sterilized petri dishes serve best as a receptacle for the sputum which should be immediately sent to the laboratory for examination. This will prevent the multiplication of the bacteria in the sputum, an undesirable feature.

The sputum should be carefully examined with a hand lens for the presence of tiny particles or flecks from one-half to three millimeters in diameter, yellowish or gray in color, which appear denser than the surrounding sputum. In some instances the fungi can only be demonstrated in such flecks and for this reason they should be selected for the microscopic study and the inoculation of the medium.

PREPARATION OF THE SPUTUM FOR MICROSCOPIC STUDY

Select, by preference, several of the above mentioned flecks and place on a clean glass slide, add one or two drops of 10 per cent sodium hydroxide and mix thoroughly. Place a cover glass over the preparation and, after an interval of three to five minutes, examine the preparation for fungi with a low and a high powered lens in a subdued light. If fungi are not found by this method it is advisable to concentrate the sputum. Place the sputum in a 50 cc. centrifuge tube and add approximately twice the amount of 4 per cent sodium hydroxide. Place the tube in boiling water for approximately five minutes, stirring the contents occasionally with a glass rod. Centrifuge for twenty minutes at high speed, decant the supernatant fluid and resuspend the sediment in 2 cc. of distilled water. Put one loopful of the mixture on a clean glass slide and place a cover glass over the preparation. The microscopic study of the unstained preparation of the sputum may suffice for the identification of the offending fungus. However, it is advisable to confirm the microscopic findings by cultural

methods. The fungi are killed at the time the sputum is concentrated and therefore the material is not serviceable as an inoculum.

PREPARATION OF MEDIA FOR THE CULTIVATION OF FUNGI

The nutritional demands of the fungi under consideration are different and for this reason several media are employed for their cultivation.

Sabouraud's Agar Medium

Sabouraud's agar is the standard medium for the isolation of fungi and is prepared as follows:

Dextrose	40.0 g.
Peptone	10.0 g.
Agar	20.0 g.
Distilled water	1000.0 cc.

Heat over steam bath or in autoclave until the ingredients are completely dissolved. Adjust the medium to a pH 5.2 to 5.5 by the addition of normal hydrochloric acid. Dispense the medium in lots of 50 to 100 cc. in glass bottles; sterilize in autoclave for fifteen minutes at 15 pounds pressure. Place the medium in the refrigerator for future use. The medium preparatory to use is melted in a steam bath or autoclave, poured in petri dishes and allowed to solidify.

Dextrose Yeast Extract Medium

Dextrose	8.0 g.
Sodium chloride	1.7 g.
Yeast extract, Difco	0.5 g.
Distilled water to make	200 cc.

Adjust the undiluted medium to pH 4 with normal hydrochloric acid. The medium is dispensed in test tubes in lots of 5 cc. and sterilized in the autoclave for fifteen minutes at 15 pounds pressure. The medium is ready for use on cooling.

Nutrient Agar

Meat extract	3 g.
Peptone	10 g.
Sodium chloride	5 g.
Agar	25 g.
Distilled water	1000 cc.

Dissolve ingredients by heating in steam bath or autoclave. Adjust the medium to pH 7.4. Dispense in 100 cc. lots and sterilize by autoclaving for fifteen minutes at 15 pounds pressure. The final reaction should be pH 7.2.

Dextrose Blood Agar

Nutrient agar	100 cc.
Blood	5 to 10 cc.
Dextrose, 20 per cent solution	5 cc.

The agar base is melted and then cooled to 45°C. The sterile dextrose solution and blood are added, the contents gently mixed and poured into petri dishes. After solidification, and following the inoculation with sputum, the plates are incubated under aerobic and anaerobic conditions at a temperature of 37°C. The colonies may first appear only after a lapse of two or three weeks. Sabouraud's is an excellent medium for the cultivation of fungi. However, it has one disadvantage in that it permits the growth of many bacteria commonly found in the sputum and one or more transplants may be required before the fungus is isolated in pure culture. This obstacle is overcome with dextrose yeast extract medium. It is also a medium that can be readily prepared and, therefore, can be utilized with advantage for the initial inoculation. The inoculated tubes should be incubated at 37°C. and inspected daily over a period of at least seven days. If growth is present it should be transplanted to Sabouraud's medium in order to observe more closely the development and the appearance of the colonies. If no colonies are observed a specimen of fresh sputum should be inoculated on glucose blood agar and cultivated under aerobic and anaerobic conditions at a temperature of 37°C.

SLIDE CULTURE METHOD

By this procedure one may witness the development and multiplication of the fungus and by this means alone may the fungus at times be identified. A few cubic centimeters of melted Sabouraud's agar are poured on a clean 2 x 3 inch glass slide, allowed to solidify and the surface inoculated with a loopful of sputum, or preferably with a culture grown in dextrose yeast extract. A clean, No. 1 cover glass, somewhat smaller than the glass slide, is placed over the surface of the medium. The cover glass is rimmed with vaseline, allowing a small opening at one end for the entrance of air and then incubated at 37°C. The prepared glass slide should be kept moist by placing it in a petri dish lined with a thin layer of moist cotton.

THE IDENTIFICATION OF THE FUNGUS

The various component parts of the fungus with their descriptive terms are somewhat difficult for the beginner to master. The illustrations of the component parts, plate II, should be helpful in this respect.

The distribution of the colonies, their size, shape and color should be noted as well as the outline of the colony and whether the surface is smooth and non-filamentous, or rough and filamentous.

Microscopic examination: Prepare an unstained slide preparation of the colony as described above. The identification of the fungus is based on the appearance of the mycelium together with the location, the number, size and appearance of the spores. Look for yeast-like budding cells and mycelia which may be septate or nonseptate, or of the racquet form. Note the presence or absence of spore heads, arthrospores and chlamydospores. It is important to bear in mind, in making comparisons, that the colony should conform to the age stated in the text for the illustrations. In some instances the size and the ap-

pearance of the colony may vary markedly with age. In making a microscopic comparison the same magnification should be used as stated in the text. The actinomyces is the only pathogenic fungus encountered in the sputum which requires a gram stain. Owing to the minute size of this microörganism, the preparation should be examined with the oil immersion lens. The recovery and identification of the pathogenic fungus from the sputum should be confirmed on several occasions, a safe and most excellent rule in mycotic diseases of the lungs.

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Plate I

ILLUSTRATIONS OF STRUCTURES THAT RESEMBLE FUNGI FOUND IN SPUTUM

The structures resembling fungi illustrated in Plate I are encountered in the examination of sputum and may prove confusing.

Fig. 1. Pollen, timothy. × 800.

Fig. 2. Pollen, maple. × 800.

Fig. 3. Cotton fibers. × 100.

Figs. 4 and 5. Elastic tissue. These are slender, highly refractile, wavy fibrils of uniform diameter and with double contour. They may appear as single strands or in bundles and frequently show an alveolar arrangement. Their ends are often frayed or split. × 200.

Fig. 6. Fat cells. × 800.

Figs. 7 and 8. Myelin globules. Colorless globules occurring in a variety of sizes and bizarre forms. × 800.

Fig. 9. Bacterial colony. Frequently found in sputum as small granules, gray or yellowish in color. They consist of a mass of either cocci or bacilli. × 400.

Figs. 10 and 11. Asbestos bodies. May occur as single structures or in small bundles and have a yellowish color. × 800.

Fig. 12. Wool fiber. × 100.

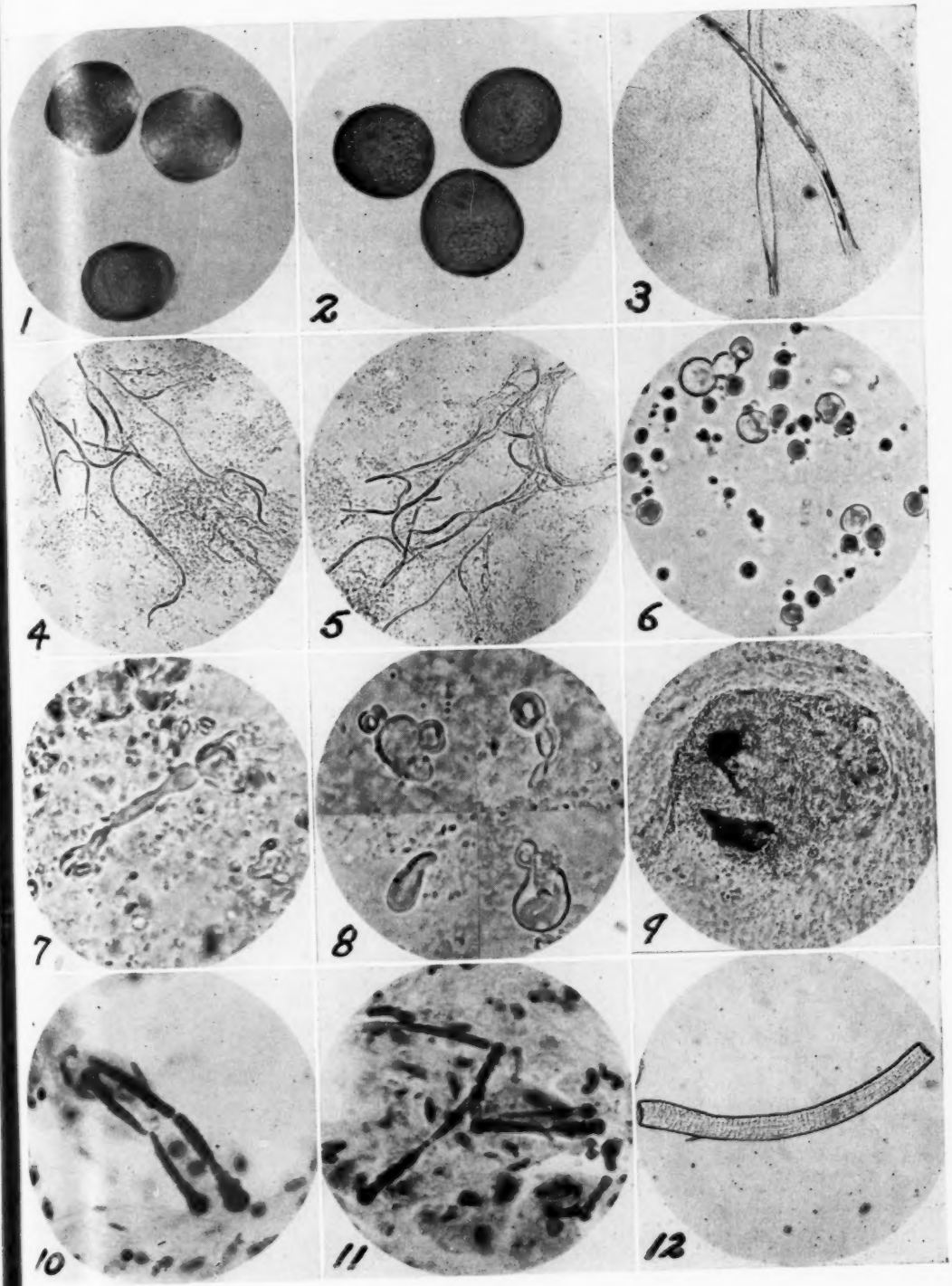


PLATE I

PLATE II

ILLUSTRATIONS OF THE COMPONENT PARTS OF THE FUNGUS TOGETHER WITH THEIR DESCRIPTIVE TERMS

FIG. 1. Thallus—or colony.

FIG. 2. Hypha—one of the filaments.

FIG. 3. Mycelia—a collection of hyphae.

FIG. 4. Mycelia—septate, having subdivisions of hyphae.

FIG. 5. Mycelia—non-septate, hyphae without subdivisions.

FIG. 6. Sporehead (Aspergillus)

(a) Conidiophore, mycelial stalk bearing conidia.

(b) Vesicle, the swollen portion of the conidiophore.

(c) Conidia, the spores.

FIG. 7. Endospores—spores formed within the parent cell.

FIG. 8. Blastospores or budding forms—spores developed by budding from the side of a parent cell.

FIG. 9. Sporophore—that part of the hypha which bears the spores.

FIG. 10. Arthrospores—segmentation of the hypha into chains of cells.

FIG. 11. Ascospores—spores formed within a sac called an ascus. The spores are limited in number to two, four or eight, depending on the species producing them.

FIG. 12. Chlamydospores—a swollen portion of the hypha. A resting spore which may be terminal, lateral or develop along the hypha.

Detailed descriptions of the component parts of the fungus are contained in standard text-books on the subject.

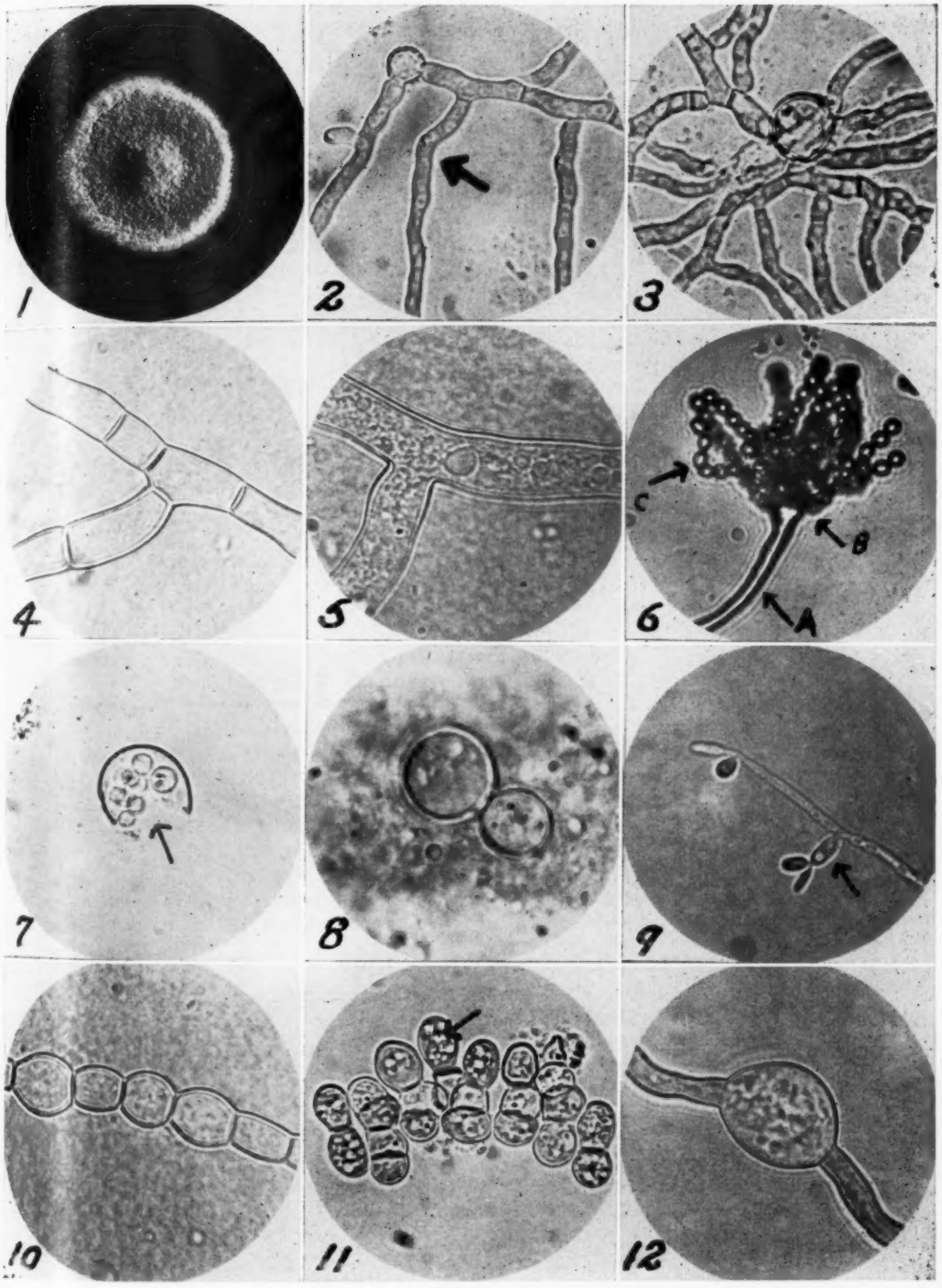


PLATE II

PLATE III

ACTINOMYCES

Actinomyces bovis gives rise to the characteristic sulphur granules, gray or yellowish in color, and varying in size, usually less than 1 mm. in diameter. When crushed between a glass slide and cover glass and examined microscopically they are found to consist of numerous smaller granules or colonies (figure 1) composed of a mass of mycelial filaments approximately 1.0 μ in diameter (figures 6, 7, 8). Around the periphery of some of these granules the filaments are arranged radially with their ends expanded into club-like forms, 10 to 20 μ in length and 5 to 8 μ in width (figures 2, 3, 4). Granules without clubbed ends may also be seen in the same preparation (figure 5). Gram stains made from crushed granules show the central filaments to be gram-positive, whereas the clubbed ends are gram-negative (figures 6, 7, 8).

Actinomyces bovis is an anaerobic organism which grows best at 37°C. The addition of glucose and blood to the medium facilitates the initial growth which varies from three to ten days before the colonies are visible. The colonies are small, round and discrete, and slowly increase in size. The surface may be finely granular or nodular and is white in color (plate IV, figure 9).

The aerobic actinomyces grow well on Sabouraud's agar medium. The colonies may be white or various shades of yellow to orange. They may develop irregular folds and concentric rings and may become covered with short aerial hyphae, assuming a chalky appearance.

In meat infusion broth both anaerobic and aerobic actinomyces develop slowly. Growth appears in from three to ten days, first noted in the bottom of the tube as small, fluffy or granular colonies which may be adherent to each other. Surface growth may be a wrinkled pellicle, at times pigmented.

Microscopically, the organisms are gram-positive pleomorphic branching filaments which often stain irregularly (figure 10). The anaerobic type is non-acid-fast, while the aerobic type may or may not be acid-fast.

Actinomycotic granules in hematoxylin-eosin stained preparations are best observed in the abscessed areas of the lung. The granules vary greatly in size. The central portion stains a deep blue color while the outer edge, or the clubbed ends, at times not prominent, stain pink (plate V). The granules, when stained by Gram's method are seen to consist of an interlacing network of gram-positive filaments, approximately 1 μ in diameter, and having a radial arrangement (plate IV, figure 11). By careful search one may observe variable sized clusters of gram-positive filaments. At times only a few short filaments are present while the larger clusters may consist of numerous filaments. Hematoxylin-eosin stained sections fail to reveal these small granules which may be overlooked unless stained by Gram's method.

FIG. 1. Unstained slide prepartion of an *Actinomyces bovis* granule in sputum. When crushed between a glass slide and cover glass, numerous smaller granules are seen. Some of these show typical clubbed ends while others do not. ×50.

FIG. 2. Granule with clubbed ends. ×200.

FIG. 3. Another granule with clubs. ×400.

FIG. 4. Edge of granule showing clubs in detail. ×800.

FIG. 5. Granule without clubbed ends. ×200.

FIGS. 6, 7 and 8. Crushed granule stained by Gram's method showing gram-positive pleomorphic filaments. Figure 6 shows a clubbed end with attached filament; figure 7 a beginning club at the end of a long filament; while a detached club is seen in figure 8.

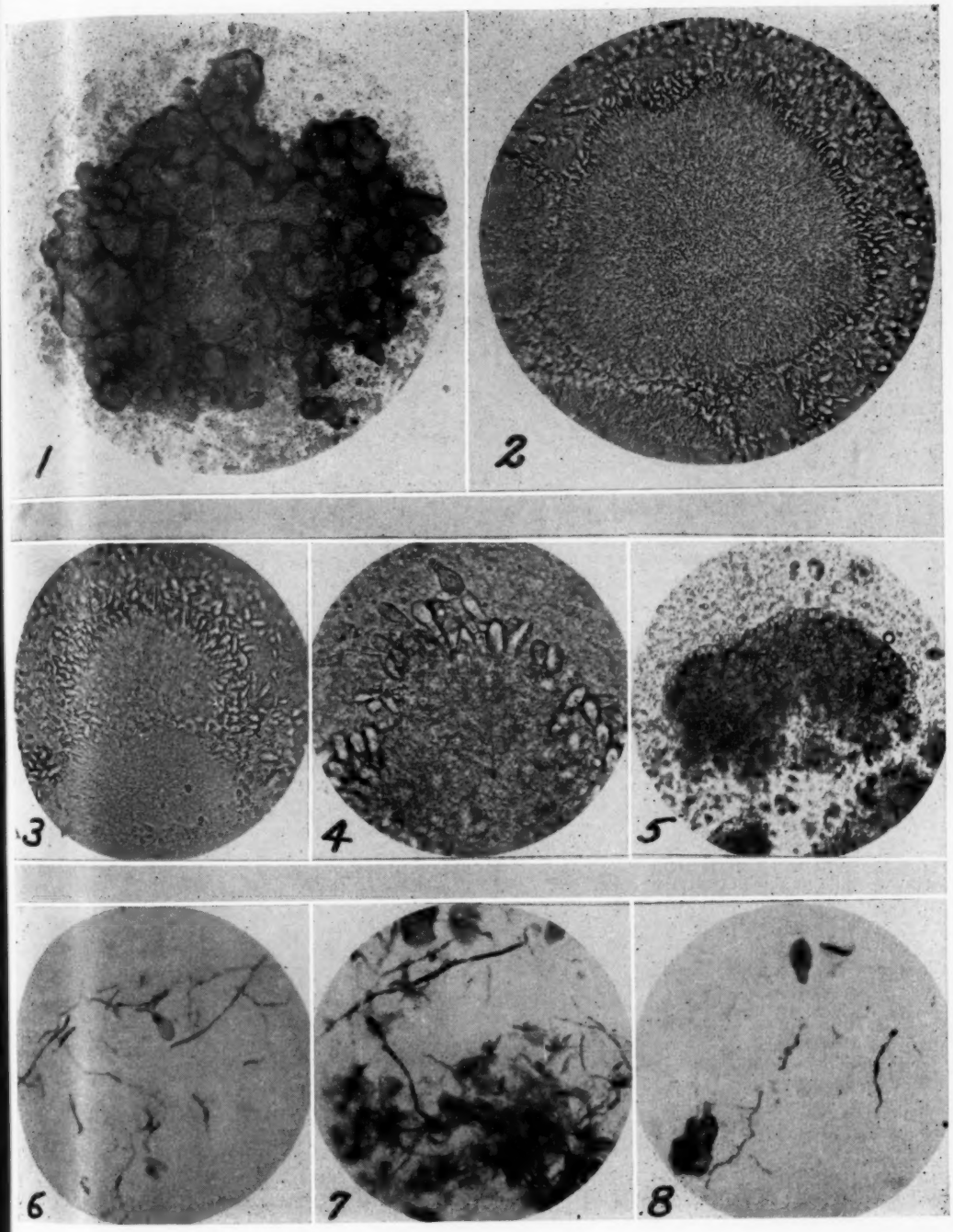


PLATE III

PLATE IV

ACTINOMYCES

FIG. 9. *Actinomyces bovis* colony grown anaerobically on dextrose blood agar, seven days at 37°C. ×10.

FIG. 10. Gram stain preparation made from a colony grown anaerobically on dextrose blood agar, seven days at 37°C. ×1000.

FIG. 11. Edge of granule in lung stained by Gram showing gram-positive branching filaments. ×1000.

FIG. 12. Edge of granule in lung with clubbed ends. Hematoxylin-eosin stain. ×800.

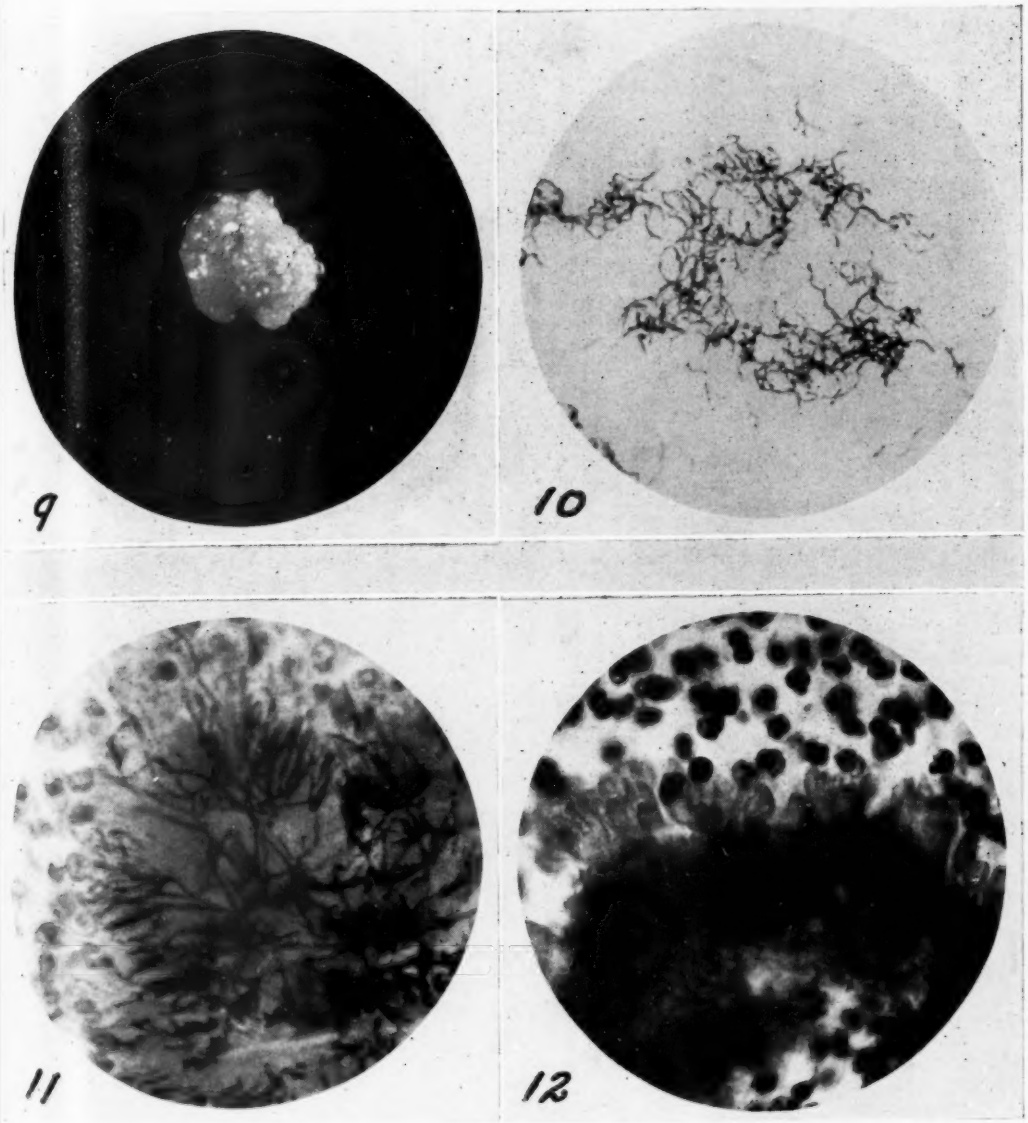


PLATE IV

PLATE V

Kodachrome illustration of an actinomyces granule in lung. ×200.

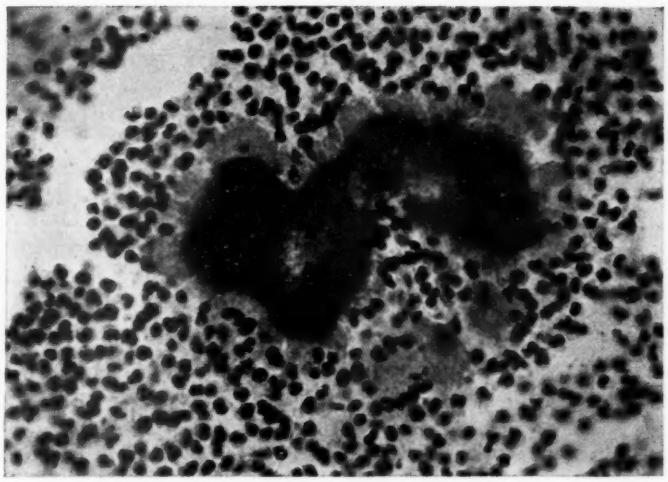


PLATE V

PLATE VI

COCCIDIOIDES IMMITIS

On microscopic examination of the fresh sputum the microörganisms appear as round, doubly-contoured spherules, varying from 5 to 70 μ in diameter. They may be seen in different stages of development. The young cells have a thin wall and contain finely granular protoplasm, while the older cells have a thicker wall and contain large numbers of small round endospores (plate XI, figure 2). Other cells appear as mere shells, only the wall remaining, at times with a few scattered spores near the ruptured cell.

Growth appears in two to ten days. On Sabouraud's agar medium, the colonies appear as small, white, fuzzy plaques, gradually becoming larger and covered with an abundance of white, aerial hyphae (plate XI, figure 2A). The color changes to brown with age. Microscopically, there is an abundance of branching, septate mycelium, with hyphae 2 to 4 μ in diameter, and giving rise to racquet mycelium and chlamydospores, 4 to 10 μ, and arthrospores 3 to 6 μ in diameter (plate XI, figure 2B).

In dextrose-yeast extract medium, the colonies appear as small, white, fluffy snowflake-like colonies at the bottom of the tube, the medium remaining clear. Microscopically, each colony appears as a mass of tangled, branching septate mycelium with an abundance of chlamydospores and arthrospores.

Plate VI sections of the lung stained with hematoxylin and eosin show the organism in various stages of development. They vary in size from 5 to 70 μ in diameter from the thin-walled younger cells to the large thick-walled double-contoured cells filled with endospores (plate VI, figures 1 to 7). The younger cells tend to stain irregularly; in some of the cells only a narrow border just beneath the capsule is stained blue, while in others the cell stains diffusely (figures 1 and 6). Spherules with a ruptured border (figure 3) are frequently observed as well as clumps of endospores without the capsule (figure 4). Spherules in giant cells may also be present (figure 7). At times peripheral spines may be observed surrounding a spherule. Spherules without endospores are almost identical with the nonbudding forms of blastomyces. However, the presence of the characteristic endosporulating spherules and the absence of budding forms are helpful in identification.

FIG. 1. *Coccidioides immitis* spherules in various stages of development. Lymph node. ×400.

FIG. 2. Mature spherule containing a large number of endospores. Lung. ×800.

FIG. 3. Ruptured spherule. Lung. ×800.

FIG. 4. A nest of freshly liberated endospores. Lung. ×800.

FIG. 5. Early development of endospores. Seen in various stages of growth. Lymph node. ×400.

FIG. 6. Spherules in a later stage. Lymph node. ×400.

FIG. 7. Two giant cells each containing five young spores. Lymph node. ×400.

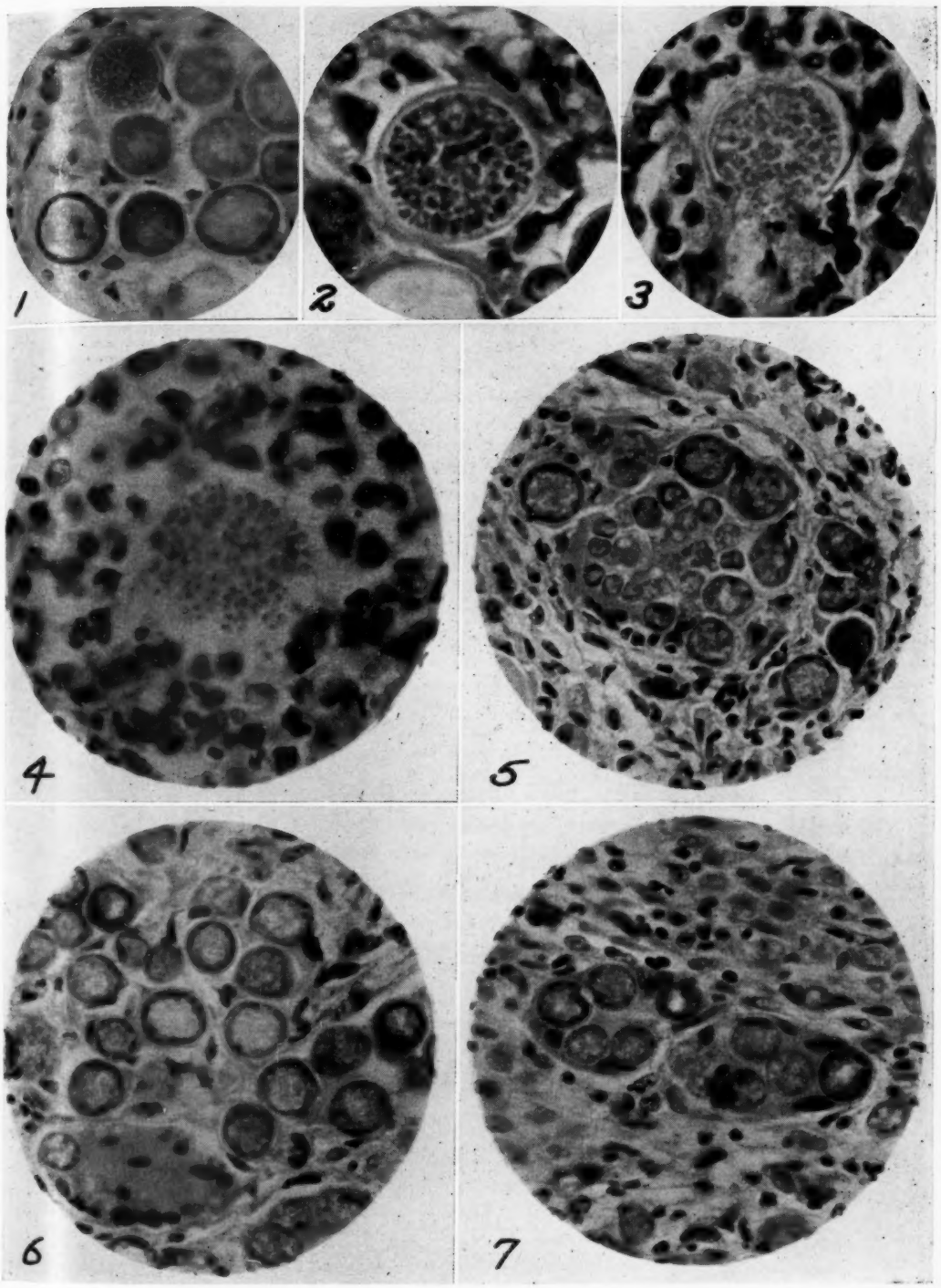


PLATE VI

PLATE VII

BLASTOMYCES

On microscopic examination of the fresh sputum the organisms appear as round or oval cells, 10 to 15 μ in diameter, having a well-marked, highly refractile, double-contoured capsule; they are found singly or in small clusters (figures 1, 2, 3). The protoplasm is granular and may contain one or more refractile vacuoles. Budding forms are always present. No mycelium occurs in sputum or pus.

Both dextrose blood agar and Sabouraud's agar media should be used. Colonies appear in three or seven days or later. On dextrose blood agar at 37°C. the colonies are yellowish-brown, wrinkled and similar to those produced by tubercle bacilli (plate XI, figure 1A). They are friable and easily broken into small fragments on the slide. Aerial hyphae are not present. Microscopically, one observes round or oval budding forms, similar to those found in sputum or pus. The cell wall is thick and highly refractile (plate XI, figure 1C).

On Sabouraud's medium the organisms appear as small, white, fuzzy colonies which gradually increase in size and become covered with fine, white, aerial hyphae (plate XI, figure 1B). Colonies usually become brown with age. Microscopically these are branching, septate, mycelia, 3 to 4 μ in diameter, to which are attached terminal and lateral conidia, 6 to 8 μ in diameter (plate XI, figure 1D).

In liquid media, such as meat-infusion broth, the organisms grow as tufted masses in the bottom of the tubes, the medium remaining clear. As the culture becomes older, a white fluffy pellicle is formed. Microscopically these organisms are similar to those grown on Sabouraud's medium.

Blastomyces in hematoxylin-eosin stained sections of lung are seen as round or slightly oval cells, 8 to 25 μ in diameter, with a thick wall and a highly refractile, double-contoured capsule (plate VII, figures 4, 5, 8). Budding cells are always present (figure 6). The organisms may be observed lying free (figure 8) or in groups (figures 4 and 5) and are frequently seen in giant cells (figure 7). The body of the cells stain light blue throughout while the capsule remains unstained.

FIGS. 1, 2 and 3. Unstained slide preparation of sputum showing the characteristic thick-walled, double-contoured, budding blastomyces spores. ×800.

FIGS. 4 and 5. Blastomyces spores in lung. ×800.

FIG. 6. Budding blastomyces spores in lung. ×400.

FIG. 7. Blastomyces spore in giant cell; in lung. ×400.

FIG. 8. Typical thick-walled spore; in lung. ×800.

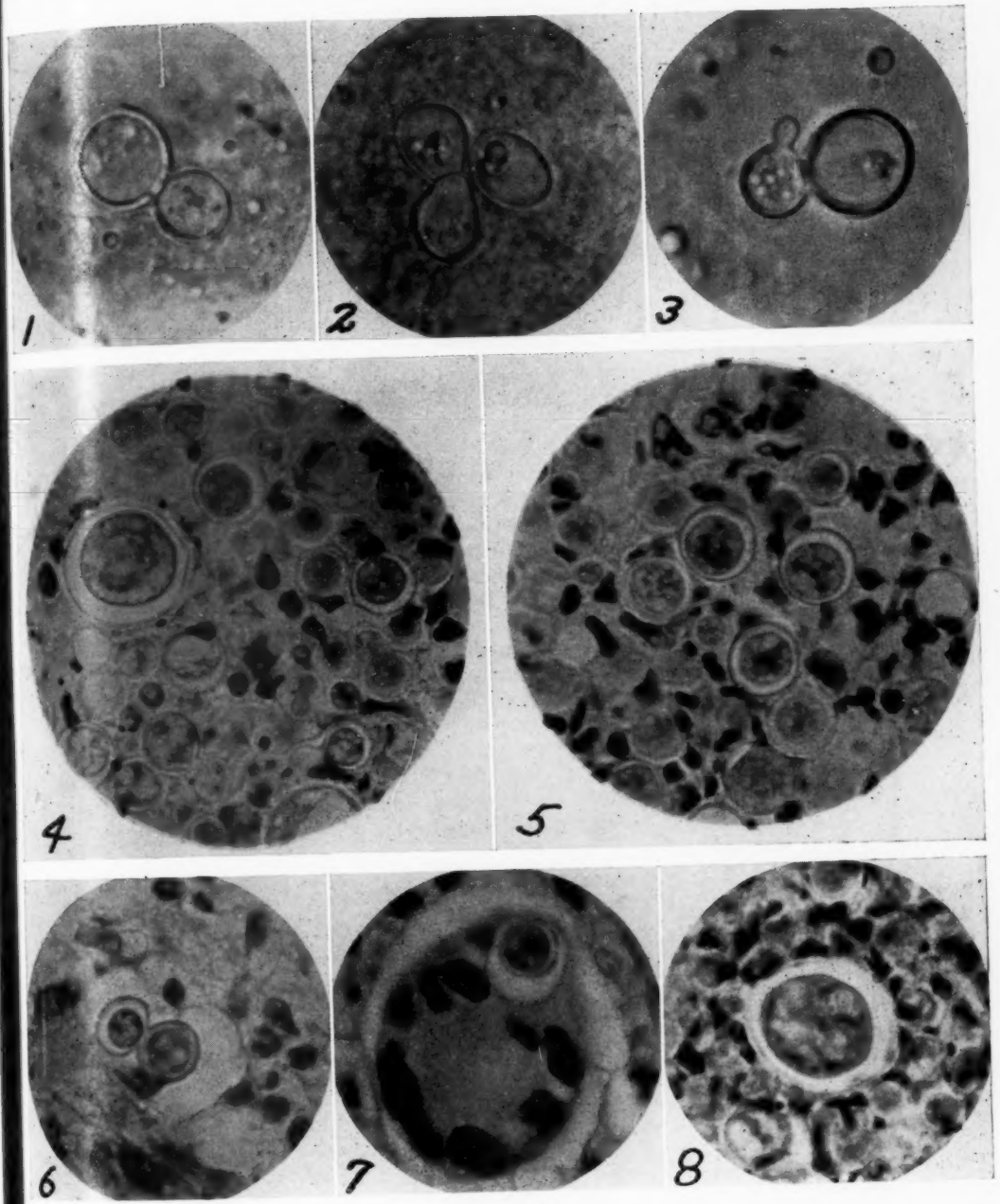


PLATE VII

PLATE VIII

HISTOPLASMA CAPSULATUM

On microscopic examination of the fresh sputum the microörganisms appear as round or oval yeast-like cells, usually with one budding cell attached, measuring 2 to 4 μ in diameter, and surrounded by a thin, well-defined refractile capsule. A large vacuole and a granule are frequently present within the cytoplasm.

There are two different forms of this fungus: the yeast-like form as seen in pus, tissue and when grown on dextrose blood agar; and the mycelial form which is seen when grown on Sabouraud's agar medium.

Growth is slow, usually requiring four to ten days at 37°C. before the colonies become visible. On Sabouraud's agar medium the colonies are white and cottony, slowly increasing in size while the aerial hyphae become more abundant (figure 1). Older cultures change from white to a light brown color. Microscopically, this microörganism gives rise to septate, branching mycelia, 2 to 4 μ in diameter. Round or pyriform spores, 3 to 10 μ in diameter, can be seen on short lateral branches along the hyphae. The characteristic identifying structures are the large, thick-walled, round or pyriform tuberculated chlamydospores, varying in size from 7 to 20 μ in diameter (figure 2).

On dextrose blood agar, the growth appears as small pasty colonies. Microscopic preparations made from these colonies exhibit small, round or oval yeast-like cells, 2 to 4 μ in diameter, similar to those found in sputum. Budding forms are present and a large granule and vacuole may be seen within the cell.

In hematoxylin-eosin stained sections of lung the organisms appear as small oval bodies, 2 to 4 μ in diameter, surrounded by a halo or capsule. They are found intracellularly in endothelial phagocytes. The central portion of the organism stains blue while the capsule remains clear (figures 3 and 4).

FIG. 1. Colonies of *Histoplasma capsulatum* on Sabouraud's agar, nineteen days at 37°C. ×6.

FIG. 2. Unstained slide preparation made from colony grown on Sabouraud's agar, nineteen days at 37°C. ×800.

FIGS. 3 and 4. Hematoxylin-eosin stained section of lung showing the organisms in endothelial cells.

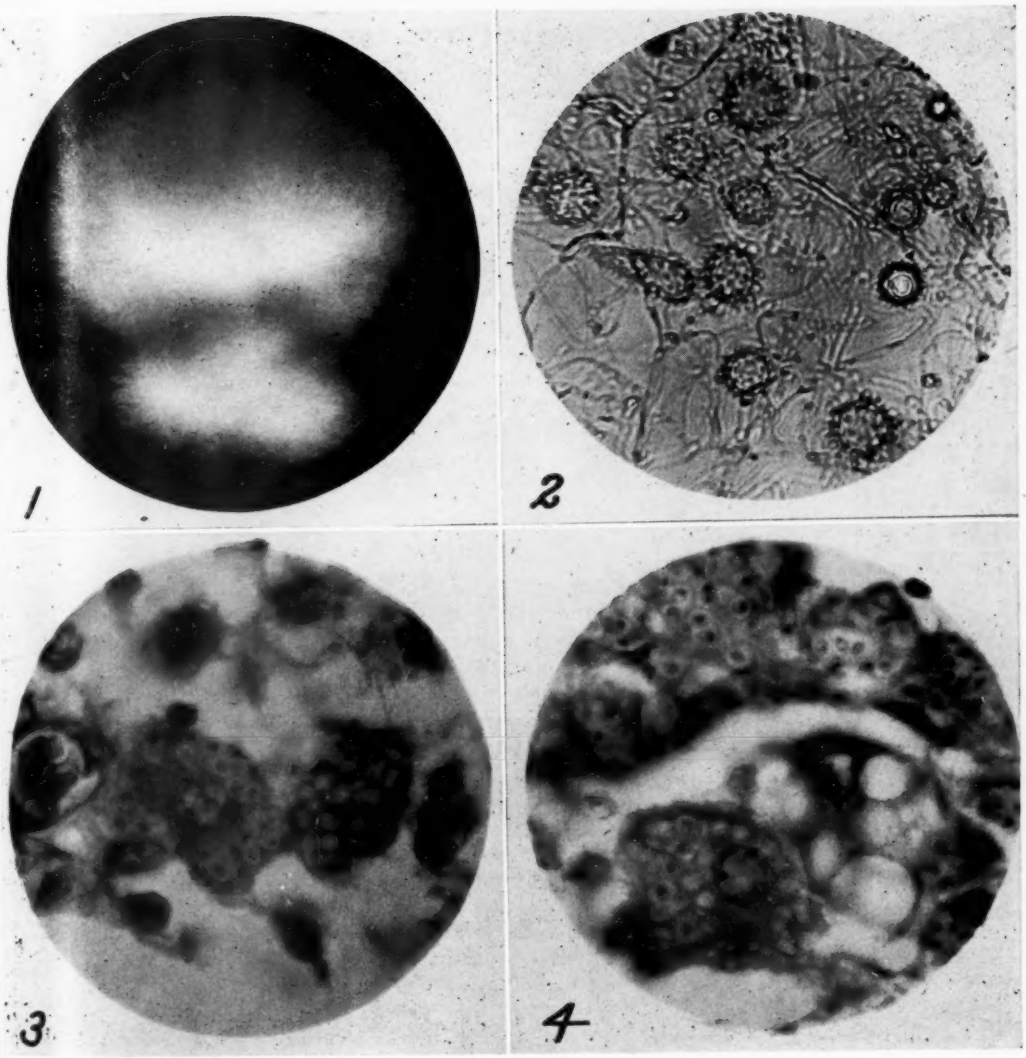


PLATE VIII

PLATE IX

CRYPTOCOCCUS

In fresh sputum the microörganisms appear as spherical cells with a thick-walled capsule, ranging in size from 5 to 15 μ in diameter. The protoplasm may contain one or more refractile granules and vacuoles. Budding forms are always present. Mycelial forms are absent.

On Sabouraud's agar medium after forty-eight to seventy-two hours' incubation, the colonies appear round, smooth, shiny and cream-white in color. They become confluent and yellowish with age. No mycelium ever develops (plate XI, figure 4A). In dextrose-yeast extract medium, growth forms a slight turbidity with a fine sediment. Pellicle and pasty ring on surface are absent.

Microscopically, the microörganisms are seen as spherical cells with well developed capsules, 5 to 10 μ in diameter (plate XI, figure 4B and plate IX, figure 1). The protoplasm is finely granular and the larger cells may contain one or more vacuoles. Budding forms are always present.

FIG. 1. Unstained slide preparation made from colony grown on Sabouraud's agar, five days at 37°C. ×800.

FIG. 2. India ink preparation made from colony grown on Sabouraud's agar, five days at 37°C. ×800.

SPOROTRICHUM

In fresh sputum the microörganisms are seen as oval or cigar-shaped bodies, from 2 to 4 μ in length and from 1 to 3 μ in width, found singly or in small clusters. They are frequently seen within pus cells. The protoplasm is finely granular and the cell surrounded by a thin capsule. The organisms resemble short, thick bacilli.

On Sabouraud's agar medium growth appears in three to ten days as white, pinhead-sized colonies which soon become surrounded by a finely-rayed fringe. Later the colonies increase in size, become convoluted, wrinkled and penetrate the medium (plate IX, figure 3). They may coalesce. Older cultures become brown to black. In dextrose-yeast extract medium growth develops slowly as small, white, fluffy colonies at the bottom of the tube, the liquid remaining clear. The colonies gradually become larger and form a thick membrane on the surface.

Microscopically these microörganisms are seen as branching, septate mycelium, about 2 μ in diameter. The spores, 3 to 5 μ in diameter, are single or grouped, and develop laterally along the length of the filaments, usually terminating them (plate IX, figure 4).

FIG. 3. Sporotrichum colony grown on Sabouraud's agar, five days at 37°C. ×4.

FIG. 4. Unstained slide preparation made from colony grown on Sabouraud's agar, five days at 37°C. ×800.

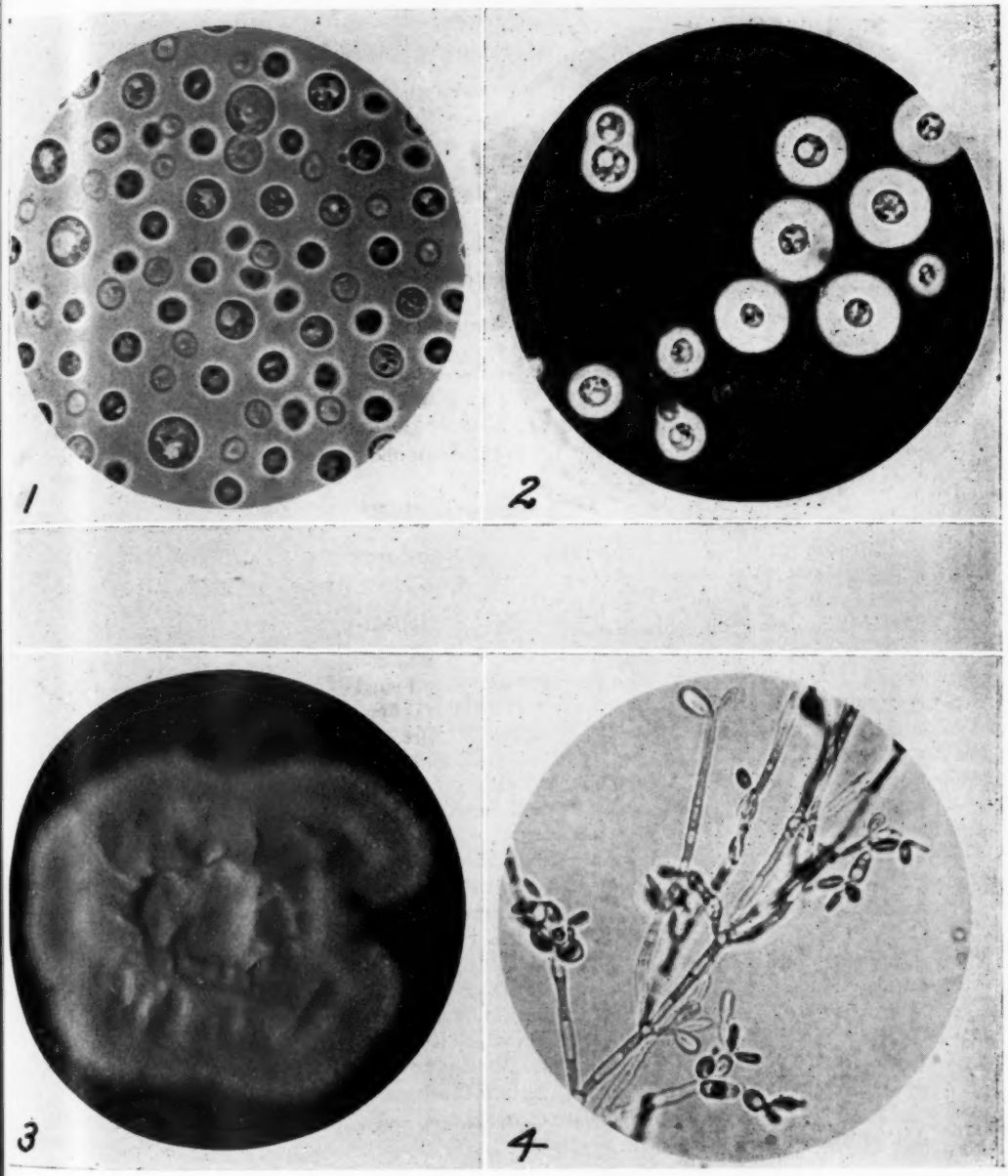


PLATE IX

PLATE X

GEOTRICHUM

In fresh sputum the organisms are seen as spherical cells, 4 to 5 μ in diameter, with a thin, double-contoured membrane. The protoplasm is finely granular and may contain a few large vacuoles.

On Sabouraud's agar medium growth appears within twenty-four to forty-eight hours. The colonies are small, white and fuzzy. They rapidly increase in size and have a characteristic radiating appearance (figure 1). These colonies are membranous and adherent to the medium. Color is white; older cultures may become yellow to amber. Dextrose-yeast extract medium becomes cloudy. Pellicle and heavy flocculent deposits are formed. Older cultures show a thick filamentous growth on the surface.

Microscopically the microörganisms exhibit septate mycelium, 3 to 7 μ in diameter, the cells of which become elongated and separate into chains of arthrospores which are spherical, ellipsoid or cylindrical in appearance, and vary in size from 4 to 9 μ in diameter and 5 to 20 μ in length (figure 2).

FIG. 1. Geotrichum colonies grown on Sabouraud's agar, four days at 37°C. Actual size.

FIG. 2. Unstained slide preparation made from colony grown on Sabouraud's agar, four days at 37°C. ×800.

ASPERGILLUS

In fresh sputum these microörganisms are seen as round or slightly oval bodies, 2 to 3 μ in diameter, and occasionally as branching septate mycelial filaments.

On Sabouraud's agar medium growth appears within twenty-four to forty-eight hours. The colonies are small, white and fuzzy. These rapidly increase in size and soon coalesce to form larger colonies (figure 3). The color of the growth, which may be green, yellow, brown or black, varies with the particular species cultured. *Aspergillus fumigatus* is the species most commonly isolated from cases resembling pulmonary tuberculosis. This species has a dark green velvety appearance on culture media. It is important to point out at this time that many saprophytic species of aspergilli are—along with the *Mucor* and *Penicillum*—the most common laboratory contaminants to be encountered in this type of work. Differential description of the many species of aspergilli can be found in the book *The Aspergilli* by Thom and Church. There are excellent illustrations of contaminating fungi found on media in *The Manual of Clinical Mycology* by Conant, Martin *et al.* In dextrose-yeast extract medium, the organisms develop in the bottom of the tube as a small filamentous mass. This gradually increases in size until growth appears on the surface of the medium forming the characteristic growth of aspergilli.

Microscopically these organisms appear as branching, septate mycelium, 2 to 5 μ in diameter. Conidiophores, which arise from large and prominent foot cells, along the mycelium, terminate in a swollen portion called the vesicle. From the latter there are given off a number of small stalks or sterigmata which in turn bear the chain of rounded conidia (figure 4). The arrangement of these component parts presents a compact mass of spores and these elements together serve as an aid in identifying the fungus.

FIG. 3. Colonies of *Aspergillus* grown on Sabouraud's agar, forty-eight hours at 37°C. Actual size.

FIG. 4. Unstained slide preparation of *Aspergillus* grown on Sabouraud's agar, forty-eight hours at 37°C. Note the spore head in the centre of the field, surrounded by conidia and mycelial filaments. ×800.

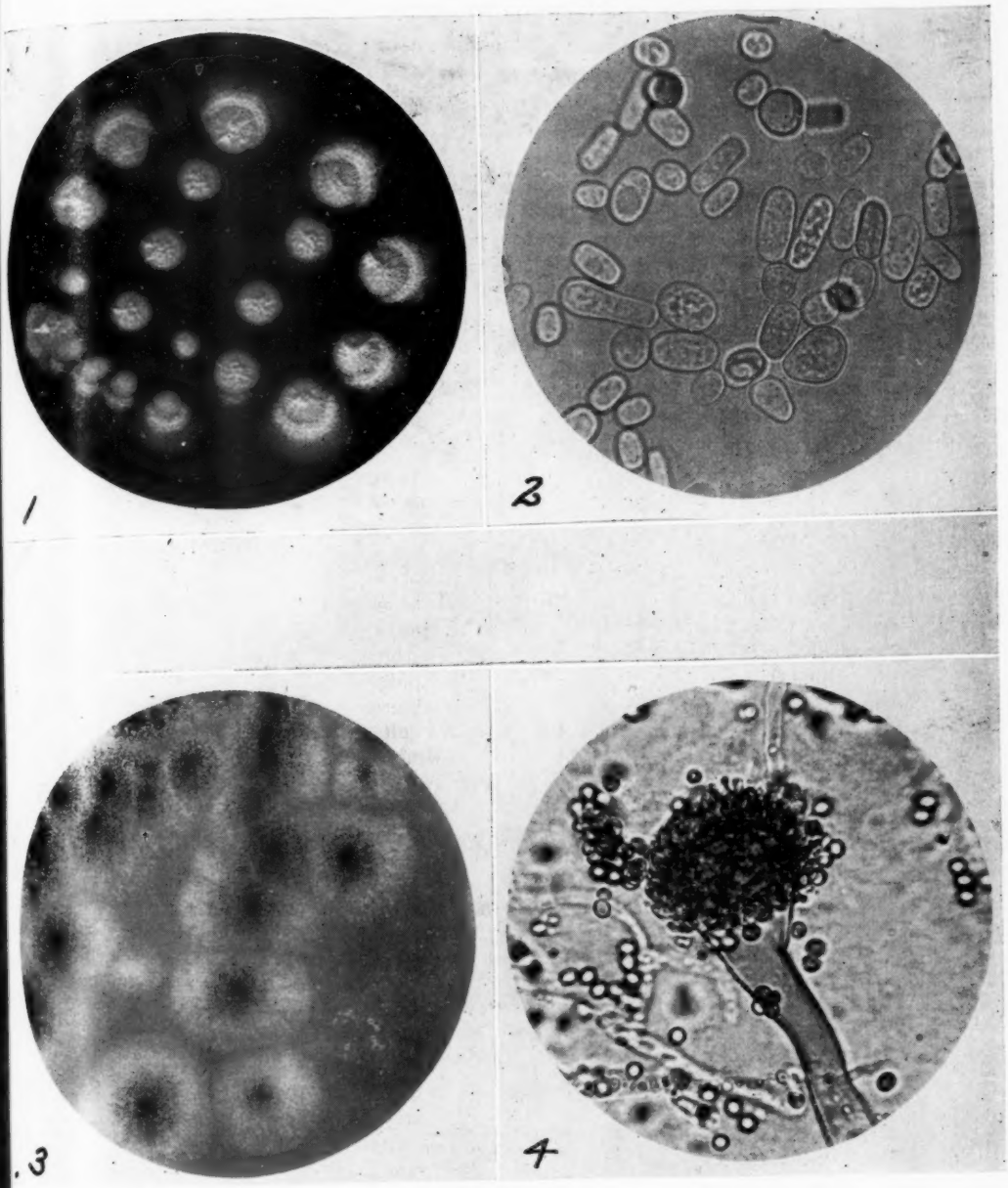


PLATE X

PLATE XI

ILLUSTRATIONS OF THE CULTURAL AND MICROSCOPIC APPEARANCE OF *BLASTOMYCES, COCCIDIOIDES IMMITIS, CANDIDA ALBICANS* AND *CRYPTOCOCCUS* FOR COMPARATIVE STUDY

Blastomyces

FIG. 1. Blastomyces spores in sputum. ×800.

FIG. 1A. Dry wrinkled type of colony grown on dextrose blood agar, twelve days at 37°C. ×6.

FIG. 1B. Wooly type of colony grown on Sabouraud's agar, twelve days at 37°C. Actual size.

FIG. 1C. Unstained slide preparation made from colony described in figure 1A, showing thick-walled, double-contoured budding cells. ×800.

FIG. 1D. Unstained slide preparation made from colony described in figure 1B showing filamentous growth with small round lateral spores. ×800.

Coccidioides immitis

FIG. 2. Ruptured *Coccidioides immitis* spherule containing many endospores in sputum. ×800.

FIG. 2A. *Coccidioides immitis* colonies on Sabouraud's agar, seven days at 37°C. Actual size.

FIG. 2B. Unstained slide preparations made from colony described in figure 2A showing chains of arthrospores and racquet mycelium. ×800.

Candida albicans

FIG. 3. *Candida albicans* in sputum. ×800.

FIG. 3A. Colonies of *C. albicans* grown on Sabouraud's agar, four days at 37°C. Actual size.

FIG. 3B. Unstained slide preparations made from colonies described in figure 3A.

In fresh sputum, the microörganisms are seen as round or oval, and occasionally elongated cells, 2 to 5μ in diameter, singly or in pairs, or in small clusters. Budding forms and short strands of mycelium, at times branches, may be present. A small nucleus within the cell is frequently seen. On Sabouraud's agar medium growth appears within twenty-four to forty-eight hours. The colonies are round, smooth and elevated, and may develop a coarse or fine mycelial fringe which penetrates into the medium. The surface may become coarsely lobulated and may develop numerous small folds over the central portion. The color may be white, gray or cream. The colonies have a pasty consistency and a strong yeast-like odor. On dextrose-yeast extract medium the solution becomes cloudy and a heavy flocculent deposit with a pasty ring and bubbly surface may form. In other cases, the medium may become cloudy with a fine layer of cells at the bottom of the tube.

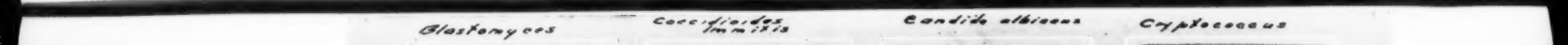
Microscopically, the organisms are seen as round or oval cells, varying in size from 3 to 9μ in diameter, with numerous budding forms present. Occasional elongated cells connected to one or more round or oval cells are seen. Large vacuoles and granules within the cells are often present.

Cryptococcus

FIG. 4. Unstained slide preparation of *Cryptococcus*. ×800.

FIG. 4A. Colonies of *Cryptococci* grown on Sabouraud's agar for five days at 37°C. Actual size.

FIG. 4B. Unstained slide preparation made from colony described in figure 4A. ×800.



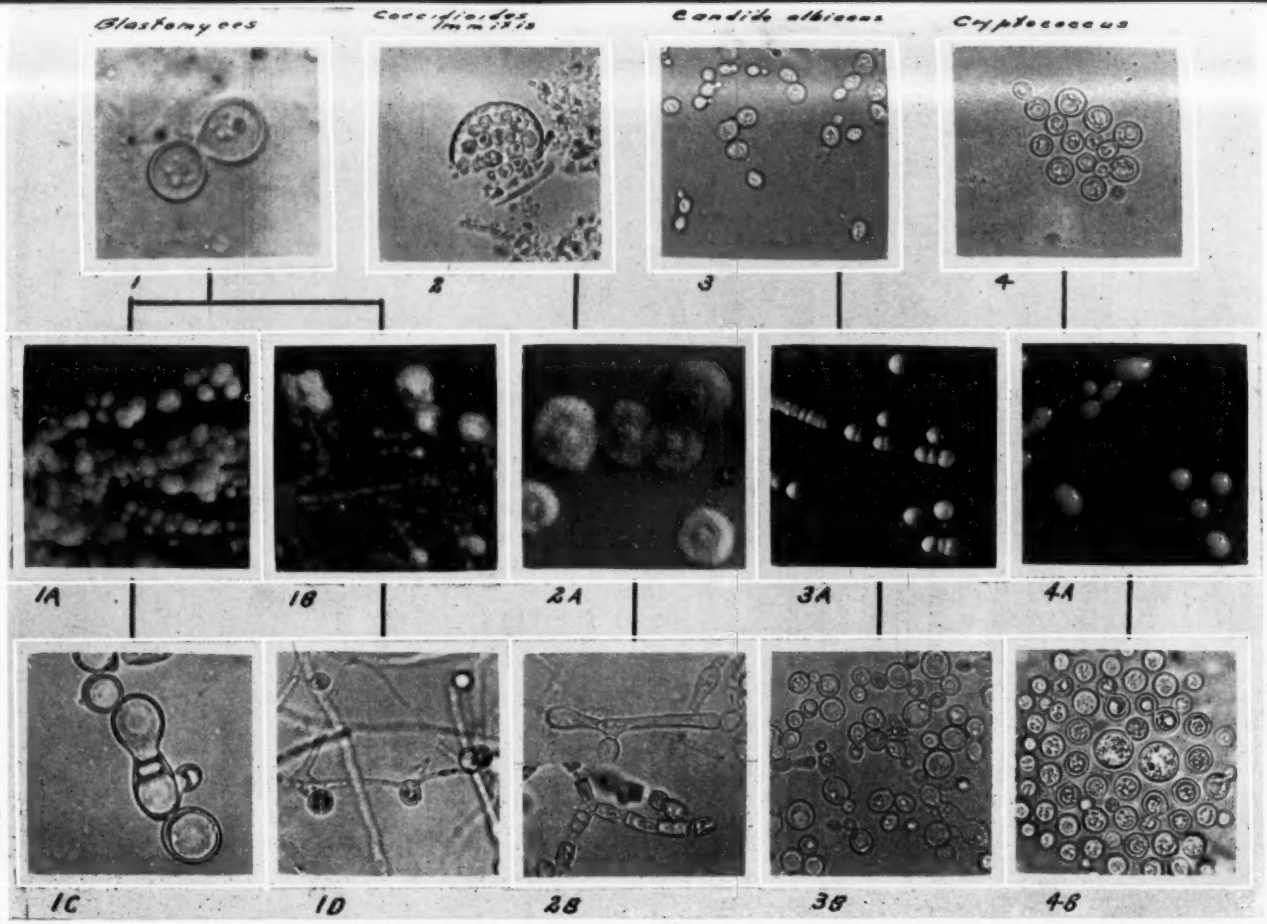

Blastomyces
Coccidioides immitis
Candida albicans
Cryptococcus
1
2
3
4
1A
1B
2A
3A
4A
1C
1D
2B
3B
4B

PLATE XI

STREPTOMYCIN AND LIPOTROPHIC AGENTS IN MILIARY TUBERCULOSIS

ALFRED C. GODWARD, JR.[1]

Miliary tuberculosis is generally considered by the medical profession as a fatal disease.

Since the introduction of streptomycin by Waksman, Schatz and Bugie (1) in 1944, the concept of therapy and the prognosis of the tuberculosis patient have somewhat changed, as indicated by the reports by Hinshaw and Feldman (2) and Hinshaw, Feldman and Pfuetze (3). In the latter paper, 12 patients with generalized hematogeneous tuberculosis are included; 6 of the 12 were still living (all but one had tuberculous meningitis) though each showed clinical signs of residual infection.

There have been a few reports of patients with miliary tuberculosis recovering spontaneously. However, laboratory proof of the infection and clinical details of such cases are not always complete.

We present a patient with miliary tuberculosis, proved by bacteriological and laboratory identification, treated with streptomycin and lipotrophic agents at the U. S. Naval Hospital, Oakland, California, in whom a complete clinical recovery appears to have resulted.

CASE REPORT

R. B., a 19-year-old Marine, private first class, was admitted to the sick-list in Hawaii in July, 1945, at which time he complained of malaise, headache, chilliness and generalized aching. His temperature was 102.6° F. Physical examination revealed splinting of the left side of his chest on inspiration. An X-ray film showed an effusion in the left pleural space. He was treated with bed-rest and thoracocentesis, and then evacuated to the United States, arriving at U. S. Naval Hospital, Oakland, on October 4, 1945.

At the time of arrival the patient was asymptomatic with the exception of mild dyspnea on exertion. Physical examination revealed dulness over the left lower chest. Laboratory tests were normal with the exception of a sedimentation rate of 20 mm. (Westergren) in one hour. Chest roentgenogram revealed a residual pleural effusion on the left side. He was treated with bed-rest and symptomatically. The sedimentation rate gradually returned to normal and the chest, according to further X-ray pictures, showed gradual clearing.

In the latter part of November the patient was sent home on a convalescent leave of two months' duration. Upon returning to the hospital on January 20, 1946, he stated that he had felt well throughout his leave. During the latter part of the leave he was employed as a taxi driver, which required long hours of daily work. A chest film at this time showed further clearing of the residual effusion and all laboratory data were normal.

Preparations were made to return the patient to duty when, on February 3, 1946, he complained of severe stabbing pains in the left chest and he had a chill. The following day his temperature rose to 102° F. and he had a second chill, bed-shaking in character.

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A chest roentgenogram was taken and typical snowstorm-like densities were seen throughout both lung fields (figure 1).

Mantoux skin tests with OT up to 1 mg. and PPD up to 0.05 mg. were negative. The sedimentation rate was 3 mm. (Westergren) in one hour. The blood count was normal.

The patient's course became progressively more stormy. Temperature, pulse rate and respiration gradually increased. He became more toxemic and uncoöperative. In the latter part of February, pleural effusion developed on the right side. Fluid withdrawn from this effusion was straw colored. The differential cell count revealed 98 per cent lymphocytes and the fluid readily formed a pellicle. A guinea pig injected with this fluid died in twenty-eight days. Autopsy of this guinea pig showed disseminated tuberculosis. Tubercle bacilli were seen in large numbers throughout all the tissues.

A urine specimen injected into a second guinea pig resulted in its death in thirty-two days and the autopsy showed generalized tuberculosis.

The patient was treated symptomatically and he received repeated blood transfusions. However, his condition became worse. Nausea and vomiting occurred after each attempted feeding. Diarrhea (eight to ten stools a day) became persistent. Changes in the sensorium became evident. The patient would cry when he was touched or when his bed-clothes were moved. On March 1, 1946, a tubercle was seen in the right retinal field approximately at the eleven o'clock position. The patient had a stiff neck on anteroflexion. No other signs of meningeal involvement were evident. Spinal puncture was done at this time and revealed that the pressure, cell count and chemistry were normal. Culture of the spinal fluid for acid-fast bacilli and guinea pig inoculation were not done.

Streptomycin therapy was started March 15, 1946, approximately six weeks after recognition of the disease, at which time the condition of the patient appeared to be terminal. His weight had dropped from 145 to 112 pounds. He had become cyanotic and required continuous oxygen inhalation. His temperature rose to 105° F. daily. His liver was palpable three finger breadths below the right costal margin. The spleen was not palpable. Pitting edema of the extremities was present and an enlarged heart with pulmonary congestion (figure 2) became manifest.

Total plasma proteins were 6.1 g. with 2.4 g. albumin and 3.7 g. globulin. The cephalin-cholesterol test was 3-plus; the urine urobilinogen was positive through a dilution of 1:640. The electrocardiogram showed flattening of the T waves in lead I, and notched QRS complexes and elevated ST segments in lead C F 4. Interpretation was that of nonlocalized toxemia of the myocardium. The blood was essentially normal and the sedimentation rate remained unaccelerated. Prothrombin time was 72 per cent of normal. Determination of calcium, phosphorous and phosphatase content of the blood and the platelet count, bleeding and coagulation time were normal.

The patient received 0.2 g. (200,000 units) of streptomycin intramuscularly every three hours, or 1.6 g. daily. In addition, he was given 5 g. of lipotrophic agents (3 g. methionine, 2 g. choline chloride) a day. The methionine was given in the form of Amigen (containing 3 per cent methionine) of which he received 100 g. a day. The Amigen was given intravenously in the early phase of therapy and orally after foods were tolerated. The choline was given orally. This treatment was given for six months, during which time he received approximately 295 g. of streptomycin and 650 g. of the lipotrophic agents. Streptomycin blood levels were not determined due to lack of equipment. The lipotrophic agents were reduced from 5 g. daily to 3 g. daily after the second month (table 1). No toxic reactions were encountered during the course of therapy.

Three days after starting the above therapy, the patient's condition improved. Nausea and vomiting ceased as did the diarrhea. His appetite returned. Emotional instability

disappeared. The chest roentgenogram began to clear after three weeks. Five weeks after therapy, the white blood count rose to 16,300 with an actual increase in the neutrophil leucocytes. The sedimentation rate rose to 28 mm. per hour (table 1).

The tubercle in the right fundus disappeared in six weeks after the start of therapy. The temperature, pulse rate and respiration slowly took a downward course with considerable physical relief to the patient. Electrocardiograms became normal after seven weeks. The plasma proteins first showed an increase of globulin and finally of albumin with a normal albumin-globulin ratio. Liver function tests became normal. Plasma proteins and liver function tests required three and a half months to return to normal levels. Abnormal liver function tests, as well as the changes in the electrocardiogram, can be interpreted as due to the presence of tubercles in the liver and the myocardium or to a generalized toxemic condition, impairing hepatic and myocardial functions. The chest film became completely clear approximately four months after beginning of therapy (figure 3).

After six months the temperature remained normal and stable. With the increase in appetite, the patient gained weight up to 165 pounds, 20 pounds over his normal weight on October 1. Guinea pigs inoculated with urine specimens, two, four and six months after start of therapy, did not show evidence of tuberculosis on autopsy. Mantoux skin tests applied six months after therapy were positive to 0.01 mg. of OT. Twelve sputa and 6 gastric washings were negative on smear, and 3 gastric washings were negative on guinea pig inoculation throughout the course of observation.

The patient was allowed to become gradually ambulatory during the eighth month. At the present time he is completely ambulatory. He presents no symptoms of active disease and all laboratory data are normal. The patient is soon to be discharged from the Hospital and will be followed in the out-patient department.

DISCUSSION

The apparent recovery of this patient can most likely be attributed to the effect of streptomycin.

The diagnosis of miliary tuberculosis was proved by recovering tubercle bacilli from the pleural fluid and the urine, and by the observation of a tubercle in the right retinal field. Twelve sputa and 6 gastric washings were negative on smear, and 3 gastric washings were negative on guinea pig inoculation. The inability to recover tubercle bacilli from the bronchial secretions was most probably due to the acuity of the hematogenous lesions and the brief duration of the disease which was probably not long enough for intrabronchial spread or rupture of pulmonary lesions into the bronchial tree.

The question as to whether this patient's disease was primary tuberculosis

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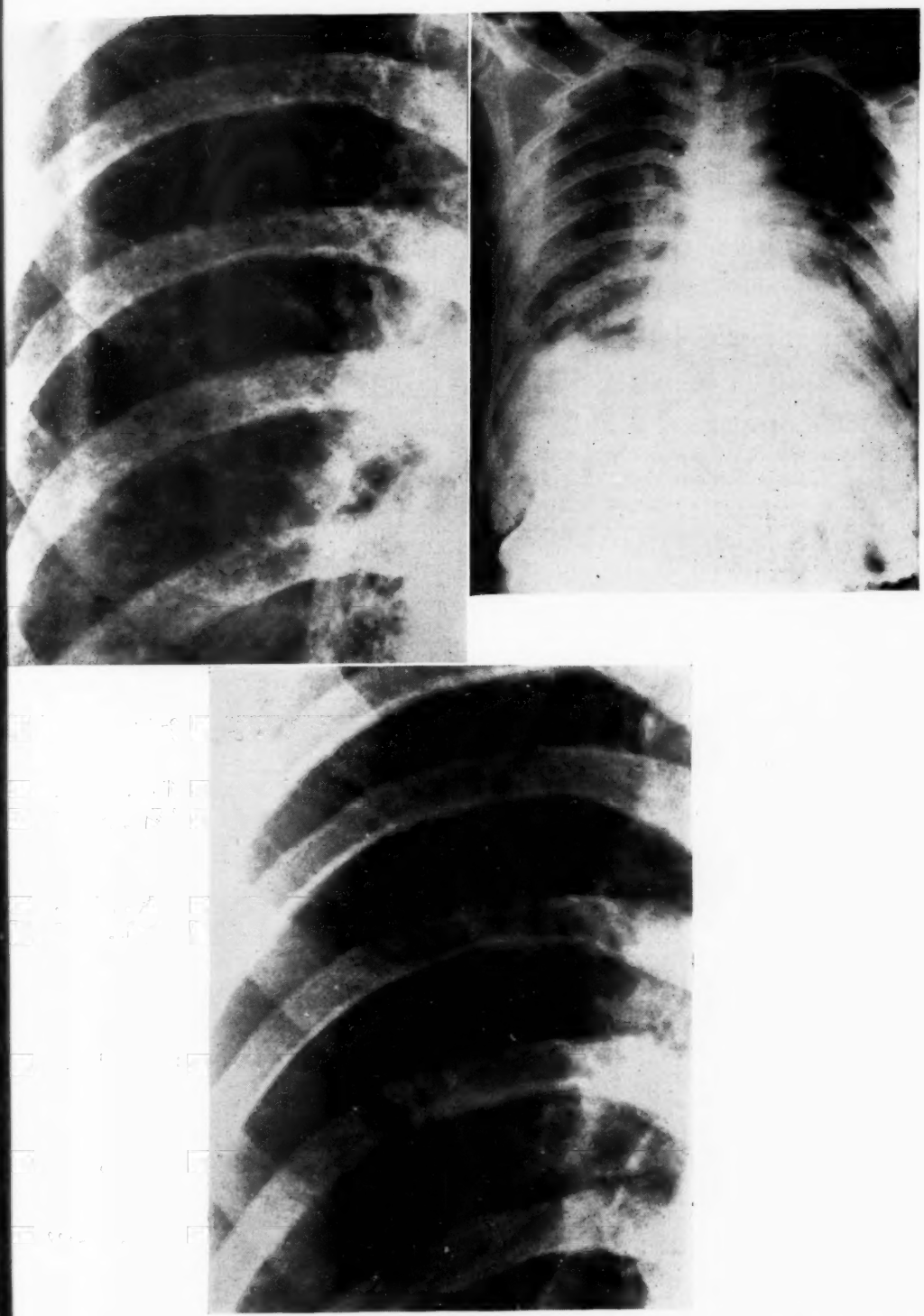
FIG. 1. (Upper left) Partial roentgenogram of chest, taken February 5, 1946, demonstrates miliary disseminated shadows, interpreted as miliary tuberculosis. A typical area is shown for demonstration of roentgenographic details.

FIG. 2. (Upper right) Roentgenogram of heart and chest, taken March 9, 1946, six days before starting streptomycin, showing enlarged heart and generalized spread of tuberculous process with an area of pneumonic consolidation in the left mid-lung field.

FIG. 3. (Lower) Film taken July 1, 1946, showing normal lung fields, three and one-half months after beginning treatment with streptomycin and lipotrophic agents. (Same area as shown in figure 1.)



FIGS. 1–3

TABLE 1

Clinical, laboratory and therapeutic data

Averages of these data by months

Temperature, F...	103.8	100.5	99.3	98.7	98.7	98.6	98.6	98.6
Pulse rate.....	132	116	110	100	80	76	72	72
Respiratory rate..	36	27	23	20	19	18	18	18
White count.....	6,300	9,600	16,300	7,400	7,300	7,600	6,800	7,100
Sedimentation rate (Westergren) in mm. per hour.....	9	17	28	14	16	12	9	6
E.C.G. (interpretation).....	General toxemia	General toxemia	N*	N	N	N	N	N
Urine urobilinogen (highest dilution positive).....	1:640	1:160	1:80	1:80	1:80	1:20	1:10	1:10
Plasma proteins (grams per 100 cc.)								
Total.....	6.1	7.8	8.5	7.9				
Albumin.....	2.4	3.0	4.5	5.2	N	N	N	N
Globulin.....	3.7	4.8	4.0	2.7				
Cephalin-cholesterol.....	3	2	1	N	N	N	N	N
Prothrombin time, per cent of normal.....	72	78	100	100	100	100	100	100
Vital capacity (normal = 4.6 lt.).....					2.2	2.8	3.2	4.0
Weight in pounds (average weight before illness 145 pounds).....	112	121	130	143	149	154	160	165
Treatment (in g. per day)								
Streptomycin.....	1.6	1.6	1.6	1.6	1.6	1.6	0	0
Methionine.....	3	3	3	3	3	3	0	0
Choline chloride..	2	2	0	0	0	0	0	0
Month.....	March	April	May	June	July	August	September	October

* N = normal.

or reinfection tuberculosis cannot be stated with certainty. The history of a tuberculous pleural effusion seven months before the onset of his hematogenous dissemination would favor the belief that the seeding occurred from localized chronic foci and that the miliary spread occurred during the reinfection phase.

The importance of the lipotrophic agents in the treatment of this case is not known. It is possible that a recovery would have resulted with the use of streptomycin alone. Hinshaw, Feldman and Pfuetze (3) report a patient with miliary tuberculosis recently started on streptomycin who still is in remission.

Lipotrophic agents were used because of the observation that they appeared to cause quiescent tuberculous infections not treated with streptomycin to exacerbate. It could be postulated that such agents have an effect on the lipoid substance of the bacillus or the fatty caseous material of the tubercle, altering the permeability or tissue environment, so as to allow the bacillus to multiply more rapidly when not checked, and rendering the patient more vulnerable to the action of specific antibiotics. Further investigaton of the combination of streptomycin and lipotrophic agents in the treatment of tuberculosis appears warranted.

SUMMARY

A case of proved miliary tuberculosis was treated with streptomycin and lipotrophic agents with apparent complete recovery of the patient.

SUMARIO

La Estreptomicina y los Agentes Lipotrofos en la Granulia

Un caso de granulia comprobada fué tratado con estreptomicina y agentes lipotrofos, obteniéndose aparentemente la curación total del enfermo.

Acknowledgments

Sincere appreciation is given to Admiral A. H. Dearing, M.C., U. S. N., Officer in Command of U. S. Naval Hospital, Oakland, California, and Captain E. F. Evans, M.C., U. S. N., Chief of Medical Service, U. S. Naval Hospital, Oakland, California, whose insight and complete coöperation made the treatment of this case possible.

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STREPTOMYCIN IN RESECTION IN PULMONARY TUBERCULOSIS

Report of Five Cases

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In 1944, Schatz, Bugie and Waksman (5) isolated streptomycin from cultures of a group of actinomycetes of the soil—*Streptomyces griseus*. During the ensuing two years Feldman and Hinshaw (1, 2, 3, 4), who made a series of well-controlled clinical and experimental studies, demonstrated conclusively the suppressive and inhibitory effect of streptomycin on the tubercle bacillus.

Streptomycin may well be effective in exerting its stabilizing influence in the preoperative and postoperative period in patients with pulmonary tuberculosis, in whom surgical intervention is done, in order to prevent the spread of the tuberculous process or to protect areas newly exposed as the result of trauma and manipulation.

The following case reports indicate what may be accomplished in the future. The plan of attack falls far short of the desired goal and was dictated by the limited supply and impure state of certain early lots of streptomycin. The impurities now have been largely eliminated and the increasing availability of supplies undoubtedly will provide the necessary amount of the drug for more extensive investigation than has been possible to date.

CASE REPORTS

Case 1: An unmarried white woman, 32 years of age, registered at the Mayo Clinic on September 15, 1945. She had been in poor health for ten years. Her illness began with an episode of fever, productive cough and night sweats in 1935. At that time an inflamed lymph node in the right cervical region was incised and the wound was drained. In 1938 examinations of the sputum were thought to reveal the presence of tubercle bacilli. By 1939 her cough was productive of small amounts of blood and in 1940 she suffered a severe pulmonary hemorrhage. In 1941 bronchoscopy was performed and an ulcer was cauterized. Her general health improved, although roentgenograms of the thorax at that time revealed an obstructing lesion in the right upper lobe bronchus. In 1942 wheezing developed and was present at the time of her examination at the Clinic. No further roentgenograms of the thorax were taken until early in 1945 when she experienced an attack of "grippe" with cough, hemoptysis and fever. She was told that the roentgenogram taken at that time revealed the presence of a pulmonary tumor.

On physical examination on her admission here the patient was a normal-looking young woman in apparent good health. No abnormalities other than those in the thorax were found. Laboratory studies revealed hemoglobin, 12.5 g.; erythrocyte count, 3,450,000; leucocyte count, 7,400; and sedimentation rate, 21 mm. per hour (Westergren method). Results of urinalysis were negative. The roentgenologist reported that fibrous and calcified tuberculosis involved the upper lobe of the right lung. A poorly defined mass was

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noted in the region of the hilum of the right lung (figure 1*a*). Repeated examinations of the sputum showed large numbers of tubercle bacilli.

On bronchoscopic examination considerable scarring on the right lateral and inferior walls of the right main bronchus was observed immediately above the orifice of the right upper lobe bronchus. The scarring produced slight narrowing of the right main bronchus. No ulceration was present. The scars probably resulted from previous cauterization with silver nitrate. The diameter of the orifice of the upper lobe was reduced to 2 mm. A small tongue of granulation tissue protruded from this orifice and a moderate amount of secretion appeared to be coming from the lobe.

The patient was hospitalized and daily intramuscular administration of 120,000 units of penicillin was begun on September 22. On September 26 the middle and upper lobes of the right lung were removed and the phrenic nerve was crushed. Bronchoscopy was performed before the patient was returned to her room. The pathologist reported that diffuse caseous tuberculosis was present in the middle and upper lobes. A tuberculous abscess, 6 cm. in diameter, was present in the upper lobe. Lymph nodes showed caseous tuberculosis. Her postoperative clinical course was satisfactory, and the wound healed by primary intention. Tubercle bacilli, however, were found repeatedly in her sputum. The source of these bacilli caused considerable concern. Postoperatively, bronchoscopy was performed and 0.5 g. of streptomycin was insufflated into the bronchial tree. No ulcerations were seen and the bronchial stump looked clean. Bronchoscopy was repeated on two subsequent occasions, but a pathological condition was not found. Nebulization with a solution containing 200,000 units of penicillin and 0.5 g. of streptomycin was begun on October 1. This treatment was given until October 13 and was repeated from November 7 to 26. In addition, 1.0 g. of streptomycin was administered intramuscularly daily from October 13 to November 15. Occasional examination of sputum still gave positive results. On November 16, in addition to nebulized streptomycin, the dose of streptomycin which was being given intramuscularly was doubled to 2.0 g. daily and this dose was given until December 12 when toxemic reaction to streptomycin became apparent. This reaction consisted of dizziness, blurring of vision and vertigo. For an additional week, after administration of streptomycin was stopped, 120,000 units of penicillin were administered intramuscularly each day. Beginning on December 15 examination of sputum for tubercle bacilli was carried out daily for eleven days and results were all negative. Cultures of gastric content obtained on December 20 were negative. About sixty days later material obtained by gastric aspiration was used for guinea pig inoculations twice and no evidence of tuberculosis was found. Cultures of the same material were negative.

On December 27, when the patient was dismissed from the Clinic, she was in good condition (figure 1*b*), save for residual dizziness, blurring of vision and slight unsteadiness. At last report on April 1, 1946, all evidence of toxemia had disappeared, her cough had cleared and her health seemed excellent although her temperature occasionally rose to 99° F. in the evening.

Case 2: A married white woman, 44 years of age, registered at the Mayo Clinic on April 20, 1946. She was known to have had pulmonary tuberculosis for five years. In 1941 the Mantoux test gave positive results and a roentgenogram of the thorax revealed a lesion of questionable activity. In 1943 cough developed and a roentgenogram of the thorax showed tuberculous involvement in the hilar region of the left lung. Although the patient remained at rest in bed, the tuberculous lesion spread. At bronchoscopic examination in 1944, an area of reddening in the main bronchus of the left lung was observed. Treatment consisted of crushing the left phrenic nerve and keeping the patient at rest in bed. One

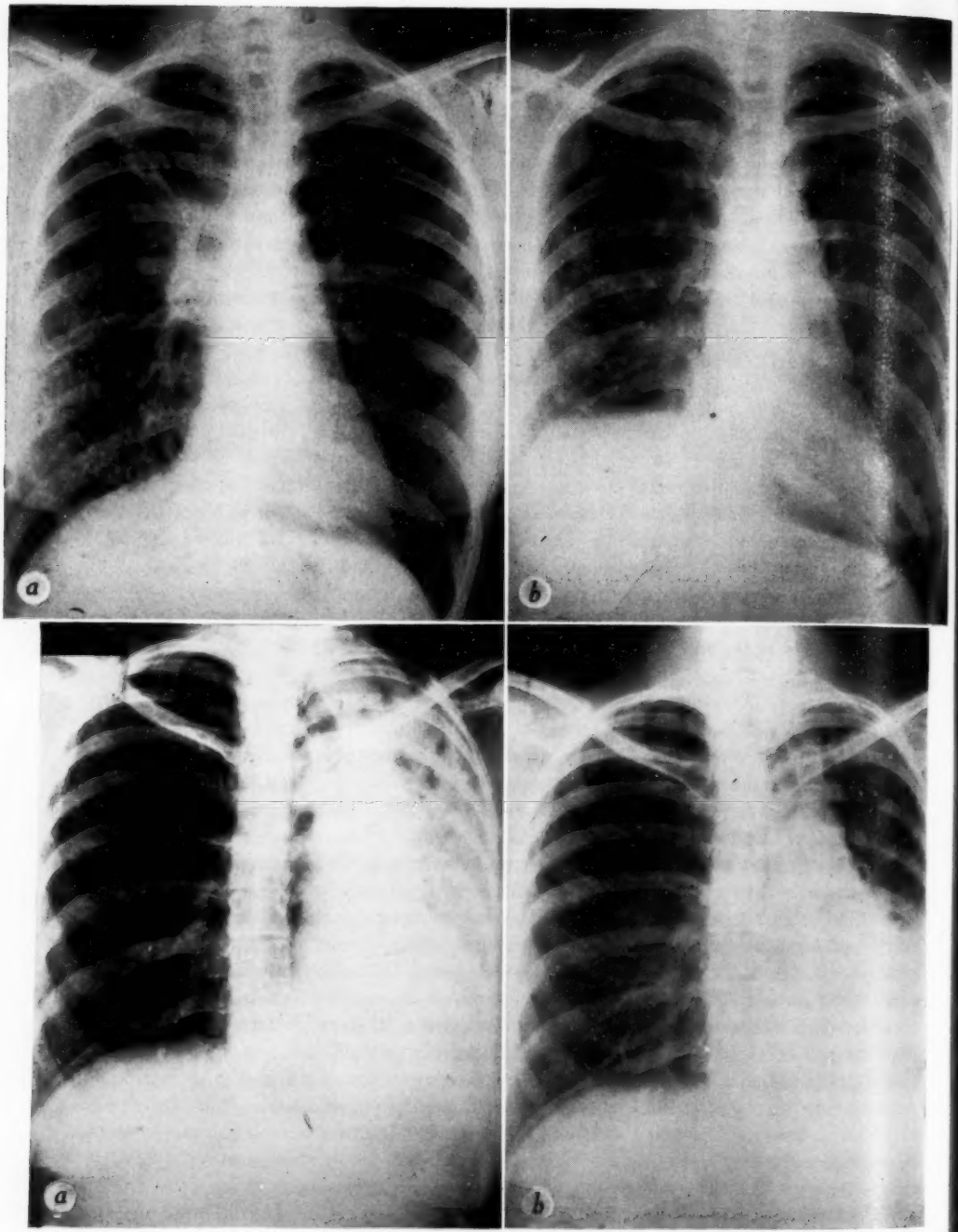

FIG. 1. (Case 1) (Upper left) *a:* Cavitation and fibrosis in right upper lobe and residual lipiodol in right lower lobe before operation; (Upper right) *b:* complete reëxpansion of the lower lobe about two months after operation.

FIG. 2. (Case 2) (Lower left) *a:* Marked bronchial stenosis with suppuration and cavitation distal to obstruction, considerable shift of mediastinal structures to the left and small area of infiltration anteriorly in the third interspace on the right at time of admission; (Lower right) *b:* clearing of left upper lobe after a period of treatment with streptomycin before operation.

year later, bronchoscopy was repeated and the findings were essentially the same as those reported previously. Diasone and penicillin produced temporary improvement. In the fall of 1945, cough recurred and she was given treatment with nebulized promin daily for five months. In the spring of 1946, bronchoscopy indicated improvement in the bronchial lesion but according to the roentgenogram there appeared to be a spread in the lower lobe of the left lung.

On admission to the Clinic the patient looked well, although she did have a slight cough, low-grade fever and signs of atelectasis of the left lung. Laboratory studies revealed that the urine was normal; hemoglobin was 13.0 g.; erythrocytes numbered 4,400,000 and leucocytes, 14,000; and sedimentation rate was 95 mm. per hour (Westergren method). Repeated examination of the sputum gave positive results. The roentgenogram of the thorax revealed a chronic diffuse inflammatory process involving the entire left lung. Multiple small cavities were noted in the left lung. There was a small area of involvement in the right anterior third interspace, marked pleural thickening and retraction of the mediastinum to the left and compensatory emphysema in the right lung (figure 2*a*).

On bronchoscopy, on April 23, the trachea and right bronchial tree appeared to be normal but the mucous membrane was pale. There was marked stenosis of the left main bronchus 3 cm. from the coryna. The stenosed orifice which was elliptical measured 3 by 6 mm. No ulceration was noted. Thick glairy secretions obtained from the region of the stenosis contained tubercle bacilli.

On April 25, daily intramuscular administration of 1.5 g. of streptomycin was begun (figure 2*b*). In addition, on April 30, daily nebulization with 0.5 g. of streptomycin was started. The patient noted light-headedness and some blurred vision on May 12 but true vertigo was not present. Nebulization was stopped but parenteral administration was continued. By May 23, dizziness had become more severe; she vomited occasionally and some nystagmus occurred when she was in a sitting position. Administration of streptomycin was discontinued. By this time no acid-fast bacilli were found when the sputum was examined. Bronchoscopy, on May 28, showed essentially the same condition as was found the last time it was performed and tubercle bacilli were found in aspirated secretions.

On June 5, intramuscular administration of streptomycin was started again in the same dosage and daily intramuscular administration of 160,000 units of penicillin was begun. The next day left pneumonectomy was performed. The left phrenic nerve was interrupted permanently and the pleural cavity was closed without drainage. Bronchoscopy was performed before the patient was taken to her room. The pathological report stated that tuberculosis of the lower lobe of the left lung and hilar lymph nodes was extensive and that the left main bronchus was stenosed. The upper lobe of the left lung apparently had not been involved in the tuberculous process, but at the time of admission was the seat of retained secretions (figure 2*a*) which apparently drained after a period of treatment with nebulized streptomycin (figure 2*b*), thus allowing the mediastinum to return to a more normal position.

The patient's postoperative clinical course was uneventful. Results of examination of the sputum were positive on June 10 and 12 but subsequently many examinations were made and results were all negative. The dose of streptomycin was increased to 3.0 g. on June 13. One week later administration of all drugs was stopped. When a specimen of fluid obtained from the left pleural cavity on June 25 was used for guinea pig inoculation evidence of tuberculosis was not found. When gastric material was used for the same study on July 2 results were again negative. The toxemic symptoms had decreased in severity but were still present.

The patient was dismissed and returned to a sanatorium early in July, 1946, and at last report, on August 26, her temperature had remained normal. She had no cough and only slight dizziness was present at times. Roentgenograms revealed that the lesion in the right lung had remained stationary and the presence of fluid in the left portion of the thorax had not caused mediastinal shift. Although she was still at rest in bed she was about to begin a program of exercise.

Case 3: A white married woman, aged 34, registered at the Mayo Clinic on May 12, 1946. She was known to have had pulmonary tuberculosis since March, 1935. At that time she had had a cough; results of examination of the sputum were positive, and roentgenological evidence of cavitation in the lower lobe of the right lung was found. Permanent interruption of the right phrenic nerve was carried out and the patient remained at rest in bed for six months and then she returned to work. She was married in 1938. In 1940 cough recurred, sputum from a cavity in the upper lobe of the left lung contained tubercle bacilli. Artificial pneumothorax on the left combined with a short period of rest in bed kept her symptom-free until July, 1943, when hemoptysis occurred suddenly. A roentgenogram revealed a fresh cavity in the upper lobe of the right lung and a well-controlled pneumothorax on the left. Artificial pneumothorax was instituted on the right side and her condition improved.

In June, 1944, the cavity on the right reopened and symptoms recurred. There followed two years of variable health. The cavity seemed to close and sputum became negative but then the cavity would reopen. Pneumoperitoneum provided some temporary benefit. Bronchoscopy in December, 1945 revealed no bronchial lesion but secretions from the right lung contained tubercle bacilli. After March, 1946, the left pneumothorax was not maintained.

When the patient was examined at the Clinic her condition presented a most difficult problem. The upper lobe of the right lung in which pneumothorax was being maintained contained an open cavity, each day she raised one ounce of sputum which contained tubercle bacilli and she had a low-grade fever, wheezing on exertion and obliterative pleuritis on the left. Some evidence of a long-standing small cavity was found in the upper lobe of the left lung under pneumothorax (figure 3*a*). She insisted that pulmonary resection be performed regardless of the outcome.

Laboratory studies revealed that the urine was normal; hemoglobin, 13.1 g.; erythrocyte count, 4,190,000; leucocyte count, 9,500; sedimentation rate, 25 mm. per hour (Westergren method); serum protein, 6.9 g.; the albumin-globulin ratio was normal. Daily examination of sputum gave positive results.

On May 15, bronchoscopy was performed but no evidence of a bronchial lesion was seen. Some purulent secretions were coming from the orifice of the upper lobe of the right lung and the mucosa in this region was somewhat red. It was thought that bronchial disease was present in the upper lobe of the right lung but evidence of it could not be seen.

Due to the lack of streptomycin the patient at first was given 200,000 units of penicillin daily by nebulization. This treatment was begun on May 18. In addition, 160,000 units were given intramuscularly. On May 31, the intramuscular administration of penicillin was stopped and a total of 2.0 g. of streptomycin was given intramuscularly daily. The daily dose was divided and given every three hours day and night.

Despite the unfavorable conditions, on June 4 the upper lobe of the right lung was removed through a posterolateral incision. This type of incision was used in all of the 5 cases herein reported. The phrenic nerve was crushed after lobectomy, and bronchoscopy for the removal of secretions was performed immediately afterward, as is routine at the

Clinic. The pathological report stated that extensive caseous tuberculosis was present and a cavity, 4 cm. in diameter, was present in the lobe.

The patient's postoperative condition was satisfactory despite the difficulty of reëxpanding the lower lobe of the right lung (figure 3*b*). Daily postoperative examinations of sputum revealed no tubercle bacilli. A specimen of pleural fluid obtained on June 13 was inoculated into two guinea pigs but no evidence of tuberculosis was found. Administration of streptomycin and penicillin was discontinued on June 17 because of lack of supply. No toxemic reactions to streptomycin were noted. Examination of gastric contents on July 1 did not reveal acid-fast bacilli.

When the patient was dismissed on July 1 no evidence of spread to either pulmonary field was found. The operative wound was healed completely. She continued to rest in a sanatorium and follow-up reports on July 15 and August 11 stated that the sputum did not contain tubercle bacilli, that evidence of spread of tuberculosis was not found in roentgenograms and that the patient was gradually beginning to exercise.

Case 4: On June 1, 1946, a white man, 44 years old, reregistered at the Mayo Clinic. When he was a patient at the Clinic in 1935 he had undergone bilateral lumbar sympathectomy for Buerger's disease. In 1945 he underwent cholecystectomy for cholecystitis with cholelithiasis.

The history of pulmonary tuberculosis dated from about February, 1942, when he was admitted to a sanatorium. At that time there was a cavity in the upper lobe of the right lung, the patient had a cough and sputum contained tubercle bacilli. During the ensuing nine months pneumothorax with closed pneumonolysis was ineffective in closing the cavity. A two-stage posterior thoracoplasty with removal of seven ribs resulted in spread of the disease into the lower lobe. Although the patient remained at rest in bed for the next year no change in his condition was noted. The right phrenic nerve was crushed in January, 1944, but this operation did not aid in closing the cavity and his sputum continued to contain tubercle bacilli. Early in 1945, complete posterior revision operation and anterior thoracoplasty in stages again failed to close the cavity. Although the patient's general condition remained remarkably good he was kept in the sanatorium for four years because of cough and presence of tubercle bacilli in the sputum.

On admission at the Clinic the patient had been moderately active for six months and respiratory reserve seemed good, but each day he was raising more than an ounce of sputum which contained tubercle bacilli.

The urine was normal; hemoglobin, 13.9 g.; erythrocyte count, 4,900,000; leucocyte count, 17,000; and sedimentation rate, 48 mm. per hour. Tubercle bacilli were found in the sputum at every examination.

Roentgenograms of the thorax indicated that thoracoplastic procedures had been performed on the right side with some regeneration of the ribs. A lesion with cavitation was present in the upper lobe of the right lung. Bronchoscopic examination showed evidence of chronic bilateral bronchitis which was more marked on the right side. Mucopurulent secretions came from the upper lobe of the right lung and the mucosa of the right upper lobe bronchus was inflamed and mildly edematous. No evidence of ulceration or stenosis was noted.

On June 4, 1.5 g. of streptomycin was administered intramuscularly and this treatment was continued daily. A week later, daily administration of 160,000 units of penicillin was added. The same day right pneumonectomy was performed by one of us (O. T. C.). The right phrenic nerve was interrupted and postoperatively bronchial secretions were thoroughly aspirated bronchoscopically. His postoperative course was without incident.

Pathological examination of the lung revealed a tuberculous cavity, 3 by 2 by 2 cm., in the upper lobe and caseous involvement of the hilar lymph nodes. In the middle and lower lobes there was extensive fibrosis but no active tuberculous foci such as were suspected preoperatively. On June 19, administration of streptomycin was discontinued because high-pitched tinnitus occurred. This cleared up shortly and the patient returned to the sanatorium on June 26. Last report, on August 2, stated that roentgenograms showed that the left lung had remained clear, temperature, pulse and respirations were normal, all signs of tinnitus had disappeared and the patient had been ambulatory for more than two weeks and was about to be dismissed from the sanatorium.

Case 5: An unmarried white woman, 29 years of age, registered at the Mayo Clinic on June 10, 1946. Although questionable roentgenological evidence of a pulmonary tuberculous lesion had been found in 1938 during a period when the patient was run-down, no treatment other than rest was advised and subsequent roentgenograms (the last in 1943) revealed no abnormalities. In July, 1945, when the patient was hospitalized because of a persistent hacking cough, roentgenological examination revealed a pneumonic shadow in the right lung. Examination of the sputum showed tubercle bacilli. She was sent to a sanatorium where pneumothorax was instituted in September. Apparently a good collapse was obtained, no adhesions were present and by February, 1946 the patient insisted on going home where she continued to rest in bed. In April, 1946 wheezing developed, cough increased, temperature became elevated and roentgenological examination revealed extensive cavitation under the pneumothorax.

On admission of the patient at the Clinic two months later she looked remarkably well although pale. She had a cough and was experiencing some chills and night sweats.

Urine was normal; hemoglobin, 13.5 g.; erythrocyte count, 4,300,000; leucocyte count, 3,700; blood urea, 24 mg.; and sedimentation rate, 113 mm. per hour. Results of daily examination of sputum for tubercle bacilli were strongly positive. Roentgenograms of the thorax showed partial right pneumothorax, apical pleural adhesions, moderate effusion and extensive saccular cavitation of the entire upper lobe of the right lung and probable involvement of the middle lobe and atelectasis of the lower lobe (figure 4). Bronchoscopic examination on June 13 showed definite narrowing of the right main bronchus with stenosis of the right upper lobe bronchus.

No streptomycin was available. Because the patient had a spiking temperature curve which daily rose to 101° F. and lesions of the so-called hot type, intramuscular administration of penicillin was started and 120,000 units were given daily.

Additional treatment became necessary and after consideration of the risks involved it was decided that the right lung should be removed "now or never." Right pneumonec-

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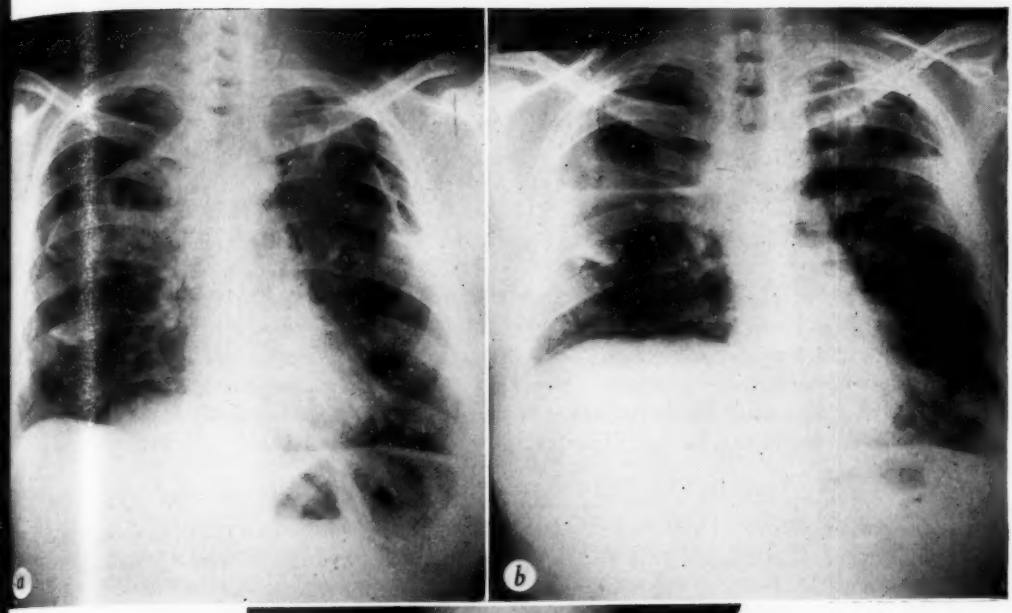
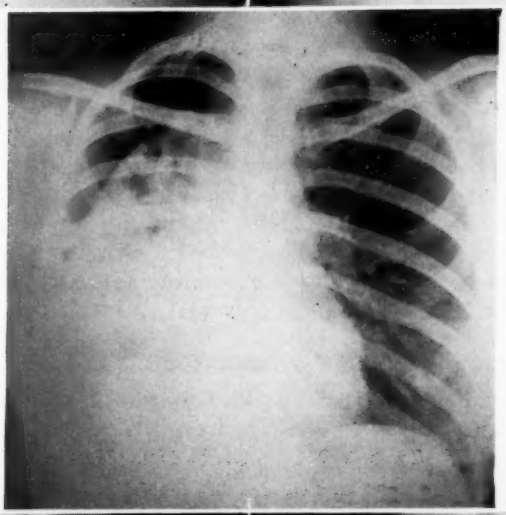
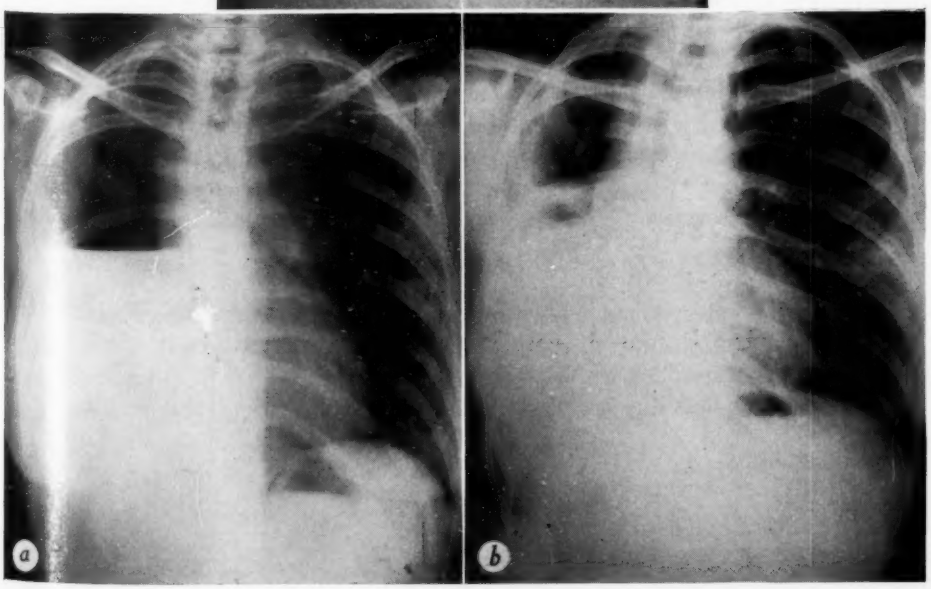
FIG. 3. (Case 3) (Upper left) *a:* Bilateral pneumothorax with a large cavity in the right upper lobe and questionable small cavity in the left upper lobe with a small amount of fluid in the left pleural space; (Upper right) *b:* incomplete reëxpansion of right middle and lower lobes after right upper lobectomy. Recent roentgenogram has shown practically complete expansion of the remaining portion of the right lung obviating possible thoracoplasty.

FIG. 4. (Case 5) (Centre) Preoperative pneumothorax on the right, marked stricture of the right main bronchus and distal suppuration and cavitation.

FIG. 5. (Case 5) (Lower left) *a:* Seventeen days after pneumonectomy; right pleural space half filled with fluid; tuberculous spread anteriorly into the left third and fourth interspaces; (Lower right) *b:* five weeks after *a*, no further progression on the left side during treatment with streptomycin. The apparent difference is due to changes in roentgenological technique.







FIGS. 3–5

tomy was performed on June 25. The right phrenic nerve was interrupted and postoperative bronchoscopy was carried out. The operative specimen showed caseous tuberculosis involving the entire lung, tuberculous and pyogenic abscesses and caseous and inflammatory involvement of all hilar nodes. The bronchial involvement extended into the right lower lobe bronchus which resulted in atelectasis. The postoperative reaction was immediate and intense with high temperature and pulse rate. Roentgenogram of the thorax on June 27 revealed an area of infiltration in the upper lobe of the left lung and the question arose as to whether this was evidence of tuberculous spread or of retained secretions and resultant nonaeration (figure 5*a*). Bronchoscopy was performed and a moderate amount of thick mucoid secretion was seen in the trachea, left main and upper lobe bronchi. This was aspirated and sent to the laboratory for culture and 1.0 g. of streptomycin was instilled into the left bronchial tree. No tubercle bacilli were found in the specimen.

A daily dose of 2.4 g. of streptomycin was then combined with the dose of penicillin. The patient recovered satisfactorily but spiking of the temperature curve recurred after eight days. The pleural space on the right was tapped on four occasions during the next week, small amounts of serosanguineous fluid were withdrawn and 100,000 units of penicillin and 0.1 g. of streptomycin were instilled. Empyema did not develop and the pleural fluid was found to be free of acid-fast bacilli. Temperature, pulse and respirations became normal two weeks later and remained so thereafter. The daily dose of streptomycin was reduced to 1.6 g. on August 5, and the administration of penicillin was discontinued. Slight vestibular symptoms occurred eighteen days after the administration of streptomycin was begun but subsided entirely although administration of streptomycin was not stopped. Our plan at the time of this writing is to continue to give streptomycin for several more weeks. Hence this treatment will have been given for three full months postoperatively. Sedimentation rate has dropped to 58 mm. in one hour and repeated roentgenographic examination has revealed no advance in the original contralateral spread (figure 5*b*).

COMMENT

It must be stated clearly that the therapeutic success in these cases is not presented in the sense of a *fait accompli*. Without question, the course in many cases parallels the course in these in which streptomycin has been used. We do think, however, that the results in these 5 consecutive cases are sufficiently encouraging to warrant the continued trial of combined surgical and antibiotic treatment. Although streptomycin will shortly be available in increasing amounts, it will be many months before supply can begin to approach demand. Under these conditions, it is suggested that, whereas treatment of established disease may require vast quantities of the drug, prevention may require considerably less and that in this prophylactic sense streptomycin may find its greatest field of service.

SUMMARY

A series of 5 case reports is presented to suggest the possibilities of combining treatment with streptomycin with radical surgical procedures in some highly selected types of pulmonary tuberculosis. While the series is not sufficient to indicate clearly that any prophylactic or therapeutic effect was realized, it is

intended to indicate the possibility of utilizing the suppressive effect of streptomycin during the crucial period before, during and after radical surgery.

It is believed that, should streptomycin be successful in preventing bronchogenic and hematogenous extension of pulmonary tuberculosis during and after operation, or should it prevent development of such a complication as tuberculous empyema, it will reduce surgical mortality and broaden the indications for radical surgical treatment of pulmonary tuberculosis.

SUMARIO

La Estreptomicina en la Resección en la Tuberculosis Pulmonar

Preséntase esta serie de cinco historias clínicas con mira a indicar la posibilidad de combinar la estreptomicinoterapia con los procedimientos cruentos radicales en ciertos casos muy seleccionados de tuberculosis pulmonar. Aunque la serie no basta para indicar netamente que se obtuviera efecto profiláctico o terapéutico, sí indica la posibilidad de utilizar el efecto supresor de la estreptomicina durante el período crítico de la cirugía radical y antes y después del mismo.

Exprésase el parecer de que, de mostrar eficacia la estreptomicina para impedir la difusión broncógena y hematógena de la tuberculosis pulmonar durante la operación y después, o para impedir la aparición de una complicación tal como el empiema tuberculoso, rabajará la mortalidad quirúrgica y ampliará las indicaciones del tratamiento quirúrgico radical en la tuberculosis pulmonar.

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STREPTOMYCIN IN EXPERIMENTAL TUBERCULOSIS*

In Vivo Sensitivity to Streptomycin of Recently Isolated Strains of Human Tubercle Bacilli and Strains of Bovine Tubercle Bacilli

WILLIAM H. FELDMAN[1] AND H. CORWIN HINSHAW[2]

The original observations on the ability of streptomycin to exert a favorable influence *in vivo* on the course of experimental tuberculosis were made on infections established by the laboratory stock strain of tubercle bacilli known a H37Rv(1). Although this strain of tubercle bacilli has been maintained on synthetic medium for many years, relatively small doses of it still have a satisfactory virulence for guinea pigs. However, from a clinical point of view it seemed important to obtain information regarding the efficacy *in vivo* of streptomycin against previously uncultured strains of tubercle bacilli obtained directly from patients who had tuberculosis. Consequently a series of experiments were done utilizing as the infective agents several recently isolated human strains of tubercle bacilli, two bovine strains of tubercle bacilli and, for comparison, strain H37Rv.[3]

METHODS

The strains of tubercle bacilli used consisted of (*1*) seven primary isolation cultures, approximately 6 weeks old, of tubercle bacilli obtained from gastric aspirations of 7 patients who had severe, progressive, pulmonary tuberculosis; (*2*) two strains of bovine tubercle bacilli, one of which was the well-known Ravenel strain, the other bovine strain being isolated from a tuberculous lymph node of a bovine animal approximately fourteen months prior to use in the present experiment; (*3*) a subculture of H37Rv. With the exception of strain H37Rv, which was grown in the synthetic medium of Proskauer and Beck, described by us in a previous article (3), the respective strains were cultured on slants of egg-yolk medium.

One-tenth milligram of each strain of tubercle bacilli was used to inoculate subcutaneously ten groups each, consisting of 14 adult male guinea pigs. The animals were caged in pairs and fed the regular laboratory ration. Starting two weeks after the animals had been inoculated, 8 animals in each of the ten groups were treated daily with 6,000 micrograms of streptomycin. The drug was injected subcutaneously in four equal doses at six-hour intervals. Treatment continued for fifty-four days. The experiments were terminated sixty-eight days after the animals had been inoculated. At the time of necropsy, material representing the following tissues was preserved for subsequent microscopic study: axillary lymph nodes, subcutis at the site of inoculation, lungs, tracheobronchial lymph nodes, liver and spleen.

RESULTS

Comparative survival times: Of the 58 guinea pigs representing the untreated controls that lived two weeks or longer, 38 (66 per cent) died during the duration

* Streptomycin utilized in this study was supplied through the courtesy of Dr. D. F. Robertson, Merck and Company, Rahway, New Jersey.

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[3] The results of these experiments have been referred to briefly in a previous publication (2).

of the experiment. A considerable number of the treated animals also died. Among 80 guinea pigs that received streptomycin, 28 (35 per cent) died. With the exception of one animal, the deaths of the untreated controls were presumed to be due to tuberculosis. The disease had disseminated widely and was present in amounts sufficient to have caused death.

In so far as signs of tuberculosis were concerned, the situation among the treated animals that died was in marked contrast to that recorded for the controls. With the exception of 4 animals that had received treatment for two days, three days, four days and eleven days, respectively, grossly visible parenchymal tuberculosis was not present at necropsy among the treated animals that died prematurely. The immediate cause of death of most of the treated animals that died was massive abdominal hemorrhage.[4]

Evidence of deterrent effects of streptomycin: The marked dissimilarity of the gross appearance of the untreated controls and the treated animals in the respective groups at the time of necropsy provided convincing evidence of the effect of the treatment. As may be noted in figures 1 to 5, proof of the pathogenicity of the respective strains of tubercle bacilli is conclusive. In most instances the disease in the control animals had involved the spleen, liver and lungs extensively with tuberculosis of the lymph nodes contiguous to the site of inoculation. The initial focus in the tissues of the suprasternal region had persisted and was progressive, with a few ulcerations commonly present. With few exceptions the disease in the untreated animals was typical of what would be expected in guinea pigs receiving subcutaneously a relatively large dose of fully virulent tubercle bacilli of the human or bovine type.

Very little tuberculosis was observed grossly in the animals in the respective groups that were treated for a minimum of fourteen days or longer. As a matter of fact, in 54 per cent of the 72 animals that received streptomycin for fourteen days or longer no lesions of tuberculosis were found either grossly or microscopically. The tuberculosis present in the remaining 46 per cent of the treated animals was for the most part minimal.

The results of the microscopic examination of the tissues obtained from untreated and treated animals in the ten groups are shown in figure 6. In this portion of the study an attempt was made to express numerically the units of tuberculosis in the various sites of predilection.[5]

An examination of the data indicates that streptomycin was equally effective in suppressing the infection produced by the seven recently isolated strains of human tubercle bacilli, the Ravenel strain of bovine tubercle bacilli and the laboratory stock strain H37Rv. The infections produced by the other bovine strain of tubercle bacilli appeared microscopically to be somewhat more resistant to the deterrent action of streptomycin than was true of the other nine strains.

[4] It appears likely that the abdominal hemorrhage was the result of injudicious restraint of the animals to facilitate medication. After measures were taken to preclude such presumed accidents few additional instances of abdominal hemorrhage have been noted.

[5] A suggested scheme for recording experimental tuberculous changes numerically has been described previously (4).

However, even in this instance the lesions present were microscopic in size and nonulcerating in character and did not reveal evidence of progression.

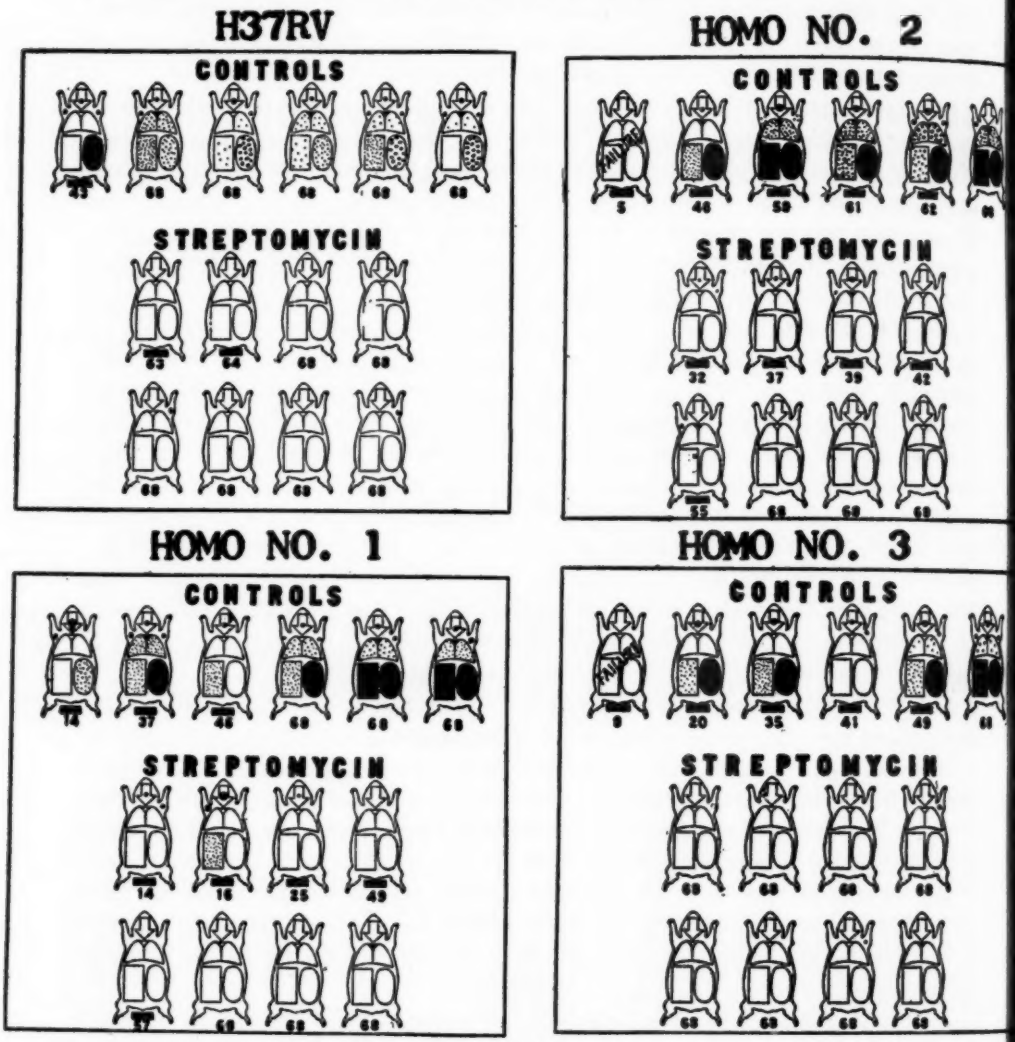

FIG. 1. (Left) Effects of streptomycin therapy in two experiments. The strains of tubercle bacilli used for inoculations were the stock strain H37Rv and an original isolation culture from a patient who had severe pulmonary tuberculosis. Guinea pigs dying before the termination of the experiment are indicated by black bars. The number under each animal in figures 1 to 5 indicates its survival time in days following infection.

FIG. 2. (Right) Effects of streptomycin therapy in two experiments. The strains used for inoculations were original isolation cultures from patients who had severe pulmonary tuberculosis.

COMMENT

This study has yielded results quite consistent with the results of the earlier experiments *in vivo* with streptomycin. The ability of streptomycin to control

tuberculous infections in guinea pigs successfully is substantial and readily demonstrable. Although the experiments were of relatively short duration the

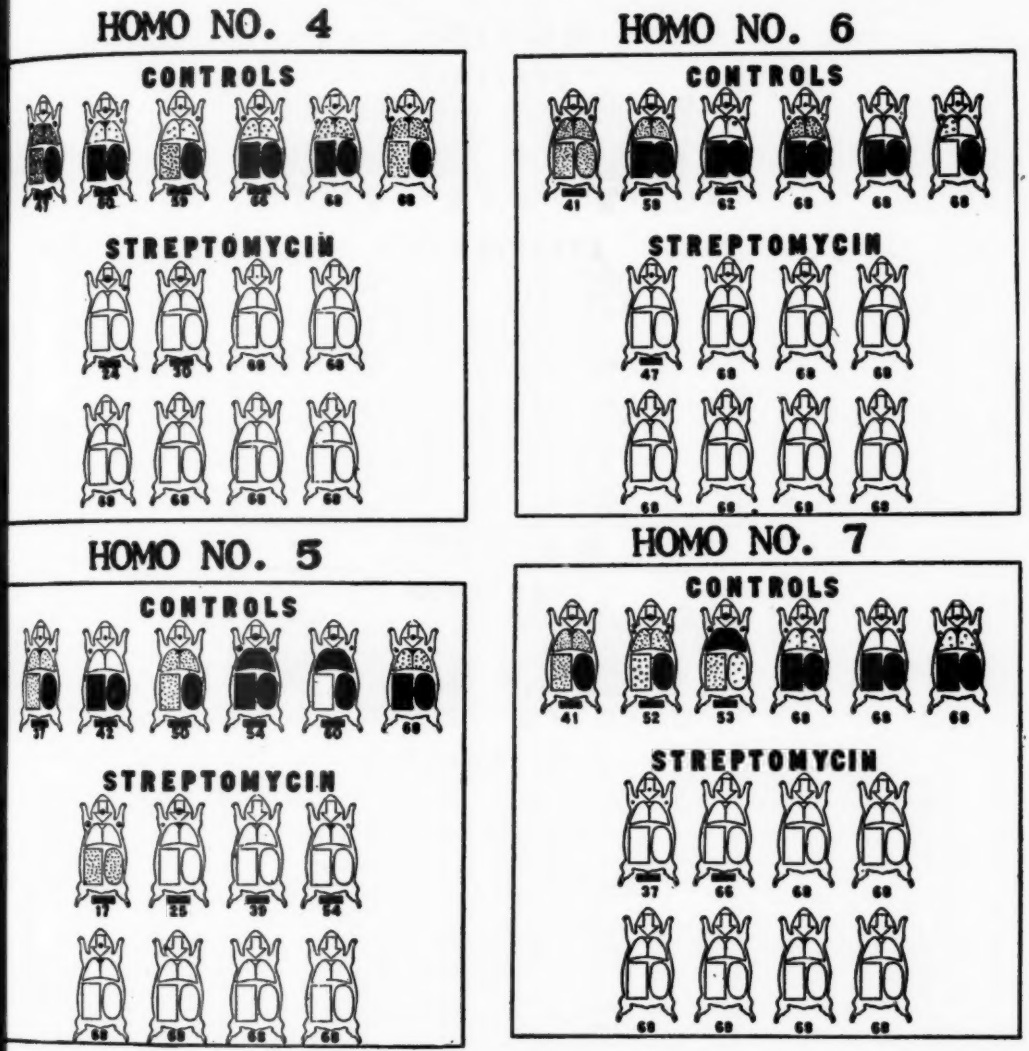

FIG. 3. (Left) Effects of streptomycin therapy in two experiments. The strains of tubercle bacilli were original isolation cultures from patients who had severe, far advanced pulmonary tuberculosis.

FIG. 4. (Right) Effects of streptomycin therapy in two experiments. The inoculum represented original isolation cultures obtained from patients who had severe pulmonary tuberculosis.

lapse of time after infection was sufficient to permit the development in the controls of an impressive amount of disease. In the treated animals the natural progression of the infectious process was markedly interfered with and as a

consequence at necropsy the regressive rather than the progressive phase of the infection was dominant.

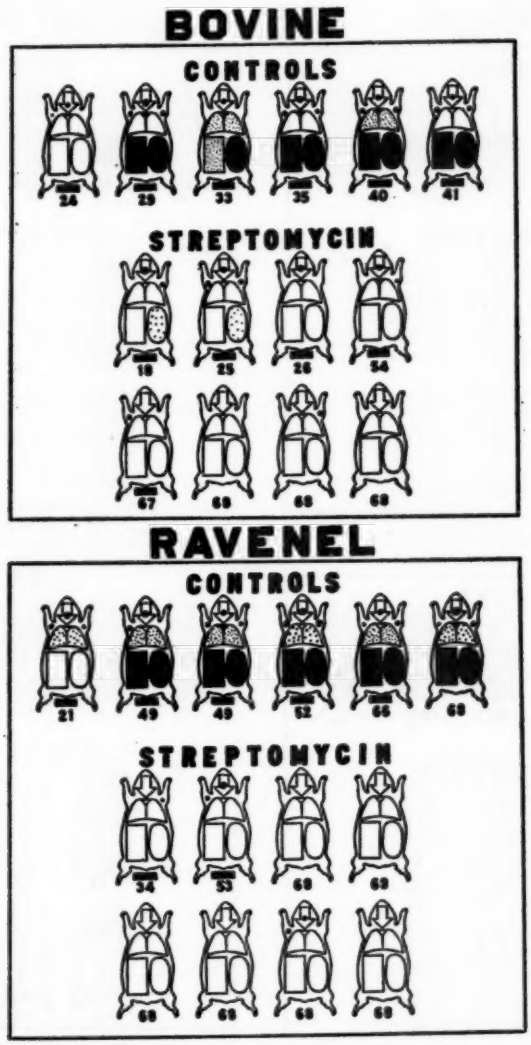

FIG. 5. Results of treating with streptomycin two groups of tuberculous guinea pigs inoculated with tubercle bacilli of the bovine type. Note the severity of the disease in the untreated controls. (Reproduced by permission of J. Roy. Inst. Pub. Health & Hyg.)

Experiments of longer duration would probably have furnished additional information regarding certain important problems related to the effect *in vivo* of streptomycin against the tubercle bacillus. However, evidence obtained after treatment for fifty-four days was sufficiently definitive to indicate that the antagonistic results of streptomycin against the laboratory stock strain

H37Rv could be obtained also against bovine tubercle bacilli and against several previously uncultured strains of tubercle bacilli obtained directly from tuberculous patients. Since the results of therapy against each of the ten strains of tubercle bacilli were comparable, confidence is maintained in the continued use of strain H37Rv as the infective agent in experimental tuberculosis.

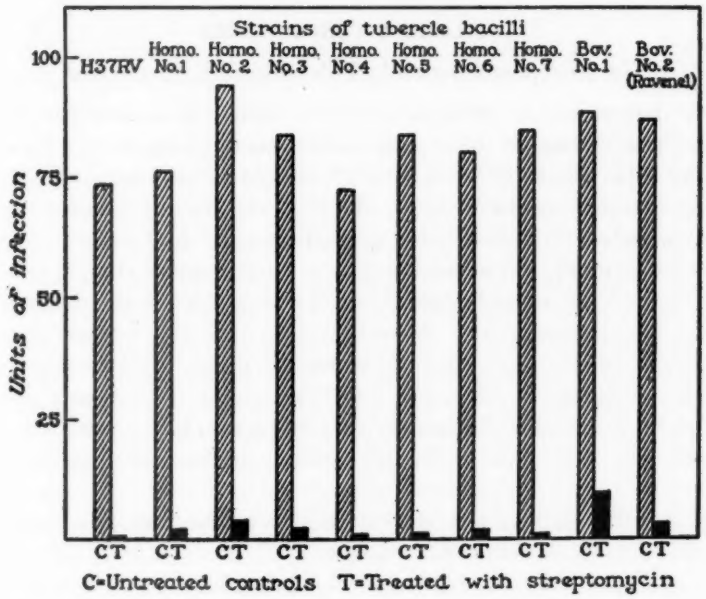

FIG. 6. Summary of relative amounts of tuberculosis, observed microscopically and expressed graphically in units of infection, produced by ten different strains of tubercle bacilli. Each strain was used to inoculate a group of 14 guinea pigs; 8 were treated and 6 were not treated. (Reproduced by permission of J. Roy. Inst. Pub. Health & Hyg.)

SUMMARY AND CONCLUSIONS

To determine the therapeutic antagonism of streptomycin to strains of mammalian tubercle bacilli other than the laboratory stock strain H37Rv, a series of 10 studies was done. Ten groups of 14 guinea pigs each were inoculated, ten different strains of tubercle bacilli being used. These consisted of seven original isolation cultures from 7 patients who had pulmonary tuberculosis, two bovine strains and, for comparison, strain H37Rv. The inoculum for each animal was 0.1 mg. of tubercle bacilli administered subcutaneously. Eight animals in each group were treated. The daily dose of streptomycin per animal was 6 mg. given in four equal doses six hours apart. Medication was started two weeks after inoculation and was continued for fifty-four days.

The results obtained from the 10 studies suggest the following conclusions:

1. The susceptibility *in vivo* of mammalian tubercle bacilli to streptomycin is not strain-specific.

2. Experimental infections produced in guinea pigs by bovine tubercle bacilli are amenable to the antagonistic action of streptomycin.

3. In chemotherapeutic experiments conclusions based on the chemotherapeutic results of infections produced by the laboratory stock strain of tubercle bacilli H37Rv constitute dependable evidence of the degree of antagonism of a given substance for tubercle bacilli of the human type.

SUMARIO Y CONCLUSIONES

La Estreptomicina en la Tuberculosis Experimental

A fin de determinar el antagonismo terapéutico de la estreptomicina a las cepas mamíferas de bacilos tuberculosos distintas de la cepa stock de laboratorio H37Rv, ejecutóse una serie de 10 estudios en que se inocularon 10 grupos de 14 cobayos cada uno, usando 10 cepas distintas de bacilos tuberculosos. Estas comprendían siete cultivos aislados primitivamente de 7 enfermos que tenían tuberculosis pulmonar, dos cepas bovinas, y para comparación, la cepa H37Rv. El inóculo para cada animal consistió en 0.1 mgm. de bacilos tuberculosos administrados subcutáneamente. Se trató a ocho animales de cada grupo, siendo la dosis diaria de estreptomicina por animal 6 mgm. administrados en cuatro dosis iguales a plazos de seis horas. La medicación fué iniciada dos semanas después de la inoculación y continuada durante cincuenta y cuatro días.

Los resultados derivados de los 10 estudios sugieren las siguientes conclusiones:

1. La susceptibilidad *in vivo* de los bacilos tuberculosos de mamífero a la estreptomicina no es específica para cepas.

2. Las infecciones experimentales producidas en los cobayos por bacilos tuberculosos bovinos ceden a la acción antagónica de la estreptomicina.

3. En los experimentos quimioterapéuticos las conclusiones basadas en los resultados terapéuticos alcanzados en las infecciones producidas por la cepa stock H37Rv del bacilo tuberculoso constituyen prueba fidedigna de la intensidad del antagonismo de una sustancia dada hacia los bacilos tuberculosos de tipo humano.

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FREQUENCY OF ADMINISTRATION OF STREPTOMYCIN*

Its Influence on Results of Treatment of Tuberculosis in Guinea Pigs

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The relatively rapid excretion from the body of known antibiotic substances has made it appear desirable to administer drugs such as penicillin and streptomycin at frequent intervals to insure the maintenance of the concentrations in the blood usually considered adequate for therapeutic effects. The presumed necessity for frequent administration of the drugs mentioned entails considerable effort and complicates what is otherwise a simple therapeutic procedure.

Attempts have been made to meet this problem by reducing the rapidity of absorption from the tissues by incorporating antibiotics in various menstrua. In the case of penicillin this has been a fairly satisfactory solution. With streptomycin the quantity of drug required for each daily dose (1 to 3 g. per day for human beings) has constituted an added complicating factor in clinical practice. Special menstrua have been proposed for streptomycin with preliminary results that seem promising (1).

In our previous studies in which streptomycin was administered to tuberculous guinea pigs the drug was injected subcutaneously every six hours (2). This interval between doses was selected more or less arbitrarily despite the fact that streptomycin could not be detected in the blood after more than three or four hours. It seemed important, therefore, to determine whether or not satisfactory therapeutic results might be obtained when the drug was administered at even longer intervals. With this objective the following study was made. Brief reference to this study was made in another publication (3).

METHOD

Sixty-four adult guinea pigs were each inoculated subcutaneously with 0.1 mg. of tubercle bacilli, human strain H37Rv. Twenty-three days later 10 of the animals (group 1) were killed for necropsy to determine the extent of the tuberculous infection. Also on the twenty-third day after inoculation, treatment of four groups (groups 3 to 6) of the infected animals with streptomycin was begun. Each group consisted of 10 animals. The 14 remaining infected guinea pigs served as untreated controls (group 2).

The total dose of streptomycin for the animals that survived until treatment was stopped in the four groups was the same; however, the frequency of administration differed. In group 3 each animal received daily 8 mg. of streptomycin in one dose. In group 4 each animal received daily 8 mg. of streptomycin in two equal doses at twelve-hour intervals. The animals in group 5 received daily 8 mg. of streptomycin in four equal doses at six-hour intervals. In group 6 the animals were treated alternate weeks; each animal received a daily dose of 16 mg. of streptomycin in four equal doses at six-hour intervals.

Treatment was terminated eighty-three days after the animals were inoculated with tubercle bacilli. The duration of treatment was sixty days.

* Streptomycin utilized in this study was supplied through the courtesy of Dr. D. F. Robertson, Merck and Company, Rahway, New Jersey.

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The presence or absence of tuberculosis in the organs of predilection was recorded at the time of necropsy. In addition, the tissues of all of the animals were subsequently examined microscopically and the numerical index of infection for each determined (table 1). This method of recording the extent and the morphological character of experimental tuberculous infections has been described previously (4).

TABLE 1

Results of microscopic determination of relative degree of tuberculosis expressed numerically

GROUP	INTERVALS OF TREATMENT	ANIMALS*	SPLEEN (MAX.: 35)	LUNG (MAX.: 30)	LIVER (MAX.: 25)	SITE OF INOCULATION (MAX.: 10)	AVERAGE INDEX OF INFECTION (MAX.: 100)
1	Not treated	10[1]	21.5	11.0	17.0	10.0	59.5
2	Not treated	14[2]	32.6	20.7	22.0	10.0	85.3
3	Once daily	9[3]	0.4	2.5	0.6	1.5	5.0
4	Twice daily	9[4]	0.6	1.4	0.11	0.12	3.2
5	Four times daily	8[5]	1.3	1.5	1.1	0.37	4.2
6	Once daily, alternate weeks	6[6]	2.1	0.66	0	3.3	6.0

* In the treated groups only animals are included that received treatment for at least three weeks.

[1] Killed on the twenty-third day following infection.

[2] Seven died before the eighty-third day following infection; survivors killed on the eighty-third day.

[3] All but 2 animals died before the eighty-third day following infection.

[4] Same as group 3.

[5] All but one animal died before the eighty-third day following infection.

[6] All but 4 animals died before the eighty-third day following infection.

RESULTS

Controls: (Group 1) The 10 guinea pigs in group 1 were killed for necropsy on the twenty-third day after being inoculated with tubercle bacilli. Evidence that the infection had disseminated widely from the site of inoculation was found in all. In all instances severe tuberculous involvement of the spleen was observed. In a few of the animals evidence of the disease was apparent grossly in the liver and lungs (figure 1*a*). Microscopically the spleen, liver and lungs of all the guinea pigs in this group were tuberculous. The average numerical index of infection for the 10 animals in this group, based on a theoretical maximal index of infection of 100, was 59.5 (table 1).

It is a reasonable presumption that the amount of tuberculosis observed in these 10 guinea pigs represented a fair indication of the virulence of the inoculum and the extent to which the disease had developed in a period of approximately three weeks. The evidence obtained—both grossly and microscopically—suggested that the animals in the groups that were treated were affected with widely disseminated, progressive, destructive tuberculosis before treatment was begun. Thus, conditions existing in the animals that were treated were formidable and not likely reversible without the aid of a potent remedial factor.

(*Group 2*) In group 2, all 14 animals received no treatment and those that were alive on the eighty-third day were killed. At necropsy the expected results of infection of guinea pigs with virulent tubercle bacilli were obtained (figure 1*b*). Of the 14 animals, 7 died, presumably as a result of the tuberculous infection, before the eighty-third day. Grossly, 6 of these had severe tuberculosis of the liver, spleen and lungs. On gross examination the liver and spleen of the seventh animal appeared to be tuberculous, but in the lungs the disease was detectable only microscopically. Of the 7 animals in group 2 that were killed on the eighty-third day, a similar degree of tuberculosis was noted grossly in 5, while

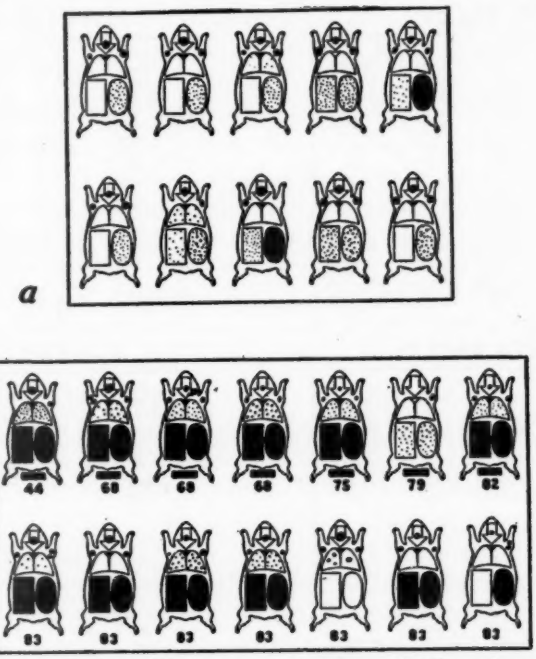

FIG. 1. The amount of tuberculosis, recorded schematically, observed grossly; (*a*) group 1, pretreatment controls; (*b*) group 2, post-treatment controls. The small numbers below each animal indicate the number of days after inoculation that death occurred. (Reproduced by permission of J. Roy. Inst. Pub. Health & Hyg., London.)

on gross examination of the remaining 2 animals the disease appeared to be limited to the spleen in one and the lungs in the other. The amount and character of tuberculosis in group 2 were determined microscopically. The average index of infection expressed numerically was determined to be 85.3 (table 1). This figure is indicative of a rather severe wide-spread infection.

Comment: The gross and microscopic findings in groups 1 and 2 constitute impressive evidence that, after inoculation of the animals with this large dose of virulent tubercle bacilli, a well-advanced progressive disease had become established when treatment of groups 3, 4, 5 and 6 was begun. Furthermore, the evidence indicates adequately that a nonreversible infection with lethal potentialities developed in animals that were inoculated but not treated.

Treated animals: (*Group 3*, treated once daily) In interpretation of the results of treatment only animals that received streptomycin for three or more weeks were considered. In group 3, none of the animals had gross signs of tuberculosis in the liver and spleen or lungs at necropsy. In some, evidence of residual disease was observed at the site of inoculation in the subcutaneous tissue over the sternum (figure 2). Microscopically the average index of infection for the 9 animals that received treatment for three weeks or longer, was recorded as 5.

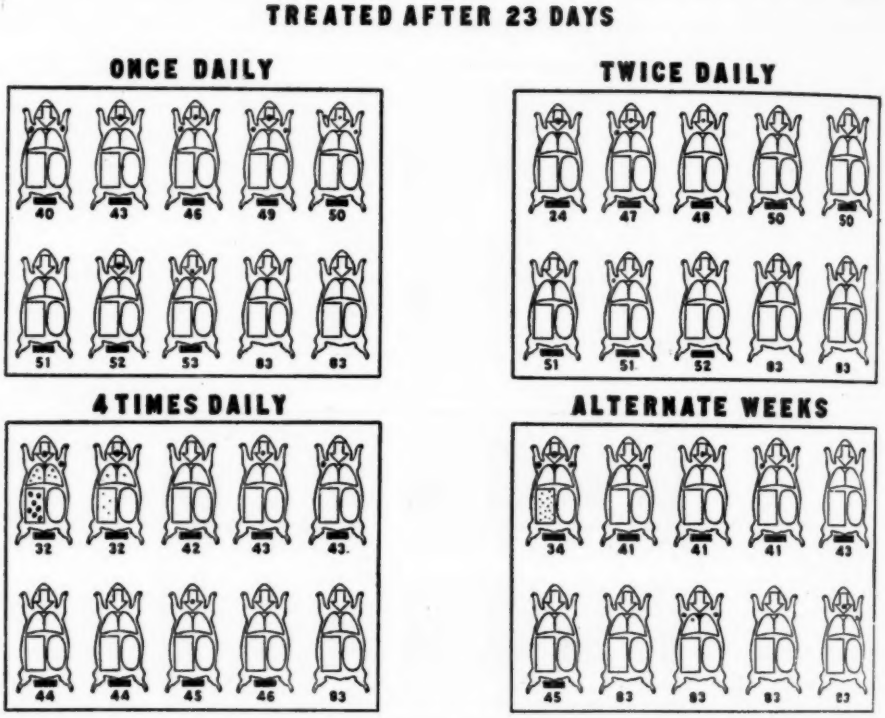

FIG. 2. The amount of tuberculosis, recorded schematically, noted at the time of necropsy in the respective groups of treated animals. The small numbers below each animal indicate the number of days after inoculation that death occurred. (Reproduced by permission of J. Roy. Inst. Pub. Health & Hyg., London.)

This was in marked contrast to the average index of infection for the group of untreated controls which was 85.3 (table 1).

Although tubercle bacilli were isolated on culture from the spleens of 7 of the 9 treated animals, in 2 instances the results of the attempts to culture tubercle bacilli from the spleen were negative. In neither of these 2 animals was tuberculosis found in the liver, spleen or lungs, grossly or microscopically.

(*Group 4*, treated twice daily) Nine animals in this group received streptomycin for three weeks or longer. On gross examination little evidence of tuberculosis was found at the time of necropsy (figure 2). Microscopically the same condition prevailed, the average index of infection for the group being 3.2

(table 1). Cultures for tubercle bacilli were made from the spleens of 8 of the 9 treated guinea pigs and all were positive for tubercle bacilli. Aside from the fact that fewer animals in group 4 had residual lesions at the site of inoculation than animals in group 3, no significant difference was apparent in the therapeutic results in the two groups.

(*Group 5*, treated four times daily) In group 5, 8 animals received streptomycin for three weeks or longer. The result of treatment in these 8 animals was quite comparable to the results recorded in group 4. Little evidence of tuberculosis was observed grossly (figure 2) and the average index of infection for the group as determined microscopically was 4.2 (table 1). Cultures of tubercle bacilli were obtained from the spleens of 7 of the animals; in one, splenic culture was negative.

(*Group 6*, treated alternate weeks) Of the 10 animals in this group living when treatment was started, 4 died before they had been treated for three weeks. Grossly little evidence of tuberculosis was observed in the 6 animals that were treated for three weeks or longer (figure 2). Microscopically, evidence of active tuberculosis of minimal extent was found in the spleen of one animal. In 2 other animals small inactive lesions were found in the spleen of one animal and in the lung of the other. The average index of infection for this group was recorded as 6. Tubercle bacilli were obtained in cultures of material from the spleen of 5 of the 6 animals that were treated. In one animal splenic cultures remained negative.

MORTALITY

Compared with previous experiences with chemotherapy in tuberculous guinea pigs, the mortality of the animals that received treatment was rather unusual. Thirty-one (77.5 per cent) of the treated animals died during the study. Eight of the animals died before they had been treated for a minimum of three weeks. Twenty-three animals that received treatment for three weeks or longer died before treatment was terminated sixty days after it was begun. Only 9 of the treated guinea pigs survived. These were killed at the end of the study. The average survival time of the animals in group 2 that died was sixty-nine days. This figure is in marked contrast to the average survival time of forty-four days for the treated animals that died before treatment was stopped.

At necropsy evidence of massive hemorrhage in the abdominal cavity was found, without exception, in the animals of groups 3, 4, 5 and 6 that died. Investigation of the cause of the hemorrhage revealed that a similar state could be produced readily if guinea pigs were restrained improperly at the time of injection. When this fact was recognized and the animals receiving treatment were handled accordingly, no further deaths occurred.

Results indicate that death of a large percentage of the animals that were treated did not preclude the accomplishment of a rather satisfactory therapeutic effect during the relatively short period of treatment. Of much importance in this respect was the rather formidable amount of disease presumably present in the treated animals when treatment was started. Examination of the 10 animals

killed before the beginning of treatment without exception showed that the infection had become well established in the liver, spleen and lungs (figure 1). It appears likely that the disease was present in a comparable degree in the 40 treated animals when treatment was started.

COMMENT

The results of these observations provide reason for further investigation of the frequency of medication in chemotherapy of tuberculosis. The results of the administration of promin intermittently to tuberculous guinea pigs have been published previously (5). In the case of streptomycin the necessity of the maintenance of appreciable concentration in the blood in order to insure therapeutic effectiveness may well be questioned.

The explanation for the therapeutic effectiveness of a single dose of streptomycin given at twenty-four-hour intervals or at six-hour intervals every other week is not apparent. Certainly the results were unexpected. A possible explanation follows. A few hours after administration of streptomycin a high percentage (75 to 80 per cent) of the drug is excreted by the kidneys. In tuberculosis perhaps a sufficient amount of the drug adheres to the surface of the bacterial cells or remains in immediate contact with the bacteria and adjacent tissues to exert a more or less constant repressive influence for a considerable time after all detectable amounts of the drug have disappeared from the blood. Perhaps the concentration of streptomycin in the tissues is as important in a slowly progressive infection like tuberculosis as is the concentration in the blood. It is possible that a single daily and rather brief exposure of the bacterial cell to streptomycin may be sufficient to so disturb the reproductive mechanism of the tubercle bacillus as to require several hours to several days for the bacillus to recover its reproductive equilibrium.

It may be presumed that during this period of antagonistic activity progression of the morbid reaction is either diminished or stopped. If the antagonistic action is repeated frequently enough, it is logical to believe that eventually the reparative factors of the involved tissues are able to attain ascendency over the pathogenic factors. When this occurs, the infection is arrested and the subsequent course of the disease will depend largely on the intrinsic susceptibility or resistance of the host.

The significance of these observations is of considerable importance. Since the results of this study failed to indicate the necessity of administering streptomycin at six-hour intervals, we have, in subsequent work, routinely administered the drug to tuberculous guinea pigs in two doses daily twelve hours apart. We use a total daily dose of 6 mg. per animal. The results of treatment of tuberculous guinea pigs on this schedule have been entirely consistent with those recorded in this report. The therapeutic effects have been in no way inferior to those obtained in earlier work in which the drug was given four times daily.

These findings should be of interest to the clinician. Possibly for certain types of clinical tuberculosis the schedule of administration of streptomycin could be

revised without adversely influencing the therapeutic results. This possibility is being investigated.

PRELIMINARY CLINICAL OBSERVATIONS

Efforts to extend these observations to clinical practice are now under way on a limited scale. Five patients who have tuberculosis have received 1.0 g. of streptomycin intramuscularly twice a day for from one to four months. No unfavorable reactions followed such injections and the usual delayed toxic effects which have been observed (6) have not varied significantly from those encountered in cases in which patients received the same daily dose in several injections. Two of these 5 patients have been treated for a sufficient period to allow observation of the therapeutic effects which were attributed to streptomycin.

It should be emphasized that clinical observations are not yet sufficiently complete to warrant alteration of the usual schedule of administration. Until they are complete we continue to recommend injections every three to six hours in treatment of clinical tuberculosis.

Due consideration should be given to the possibility that infrequent administration of streptomycin might facilitate the appearance of drug resistant strains of tubercle bacilli. No observations have been made which would support this suggestion. On the contrary, it has been observed that frequent administration of large doses of streptomycin does not prevent the appearance of drug resistant strains of tubercle bacilli in certain cases.

SUMMARY

Observations of the influence of different schedules of administration of streptomycin on treatment of tuberculosis in 64 guinea pigs are recorded. All of the animals were inoculated subcutaneously with 0.1 mg. of tubercle bacilli, human type (H37Rv). Extensive tuberculosis developed in 10 animals that were killed on the twenty-third day after inoculation. Four groups of 10 animals each were used to determine the effect of different schedules of administration on treatment. The total amount of streptomycin administered was the same for each animal that lived till the eighty-third day. Treatment was started on the twenty-third day after inoculation. In groups 3, 4 and 5, the daily dose was 8 mg. The schedule of administration of streptomycin varied. In group 3 the animals received the drug in one dose given daily; in group 4 two doses were given daily; in group 5 the drug was given four times daily at six-hour intervals. In group 6 the daily dose of streptomycin was doubled and administered every six hours. However, the animals in group 6 were treated only alternate weeks. A group of 14 infected guinea pigs (group 2) served as untreated controls. The duration was eighty-three days. In addition, a few observations on administration of streptomycin twice daily to patients with clinical tuberculosis are mentioned.

The data concerning the marked efficiency of streptomycin in combating previously established tuberculosis in guinea pigs were consistent with data reported previously.

In our study of tuberculous guinea pigs administration of streptomycin at frequent intervals during each twenty-four hours was not essential to successful therapeutic results. In tuberculous guinea pigs administration of streptomycin twice daily at twelve-hour intervals seemed adequate. The eventual suppression of the disease was striking and consistent.

When guinea pigs were inoculated with tubercle bacilli three weeks before treatment was started, the condition which developed was markedly improved within a relatively short time (three to four weeks) by administration of streptomycin.

The results suggest the importance of a critical examination of the present schedule of streptomycin therapy in clinical tuberculosis. In the absence of adequate data it would appear advisable at present to continue to administer streptomycin at frequent intervals in cases of tuberculosis. However, large doses given infrequently are well tolerated by human beings.

SUMARIO

La Frecuencia de la Administración de la Estreptomicina. Su Influjo sobre el Resultado del Tratamiento de la Tuberculosis en el Cobayo

Preséntanse observaciones acerca del influjo de distintos horarios de administración de la estreptomicina en el tratamiento de la tuberculosis en 64 cobayos. A todos los animales se les inoculó subcutáneamente 0.1 mgm. de bacilos tuberculosos de tipo humano (H37Rv). En 10 animales matados al 23° día de la inoculación se observó tuberculosis extensa. Usáronse cuatro grupos de 10 animales cada uno para determinar el efecto de diversos horarios de administración sobre el resultado del tratamiento. La dosis total de estreptomicina administrada fué idéntica para cada animal que sobrevivió hasta el 83° día. El tratamiento se inició el 23° día consecutivo a la inoculación. En los grupos 3, 4 y 5 la dosis diaria fué de 8 mgm., variando el horario de administración de la estreptomicina. En el grupo 3 los animales recibieron la droga en una dosis diaria, en el grupo 4 en dos dosis diarias, y en el grupo 5 en cuatro dosis diarias a plazos de seis horas. En el grupo 6 se dobló la dosis diaria, administrándose cada seis horas, pero sólo se trató a los animales en semanas alternadas. Un grupo (el 2) de 14 cobayos infectados constituyó los testigos no tratados. El experimento duró 83 días. Menciónanse, además, algunas observaciones relativas a la administración de la estreptomicina dos veces diarias a enfermos con tuberculosis clínica.

Los datos referentes a la pronunciada eficacia de la estreptomicina para combatir una tuberculosis previamente establecida en los cobayos armonizan con los presentados anteriormente.

En este estudio de cobayos tuberculosos la administración de estreptomicina a plazos frecuentes cada 24 horas no resultó indispensable para el éxito terapéutico, pareciendo adecuada la administración dos veces diarias a plazos de 12 horas. La supresión eventual de la enfermedad fué notable y constante.

Cuando se inoculó a los cobayos con bacilos tuberculosos tres semanas antes de iniciar el tratamiento, el estado evocado mejoró decididamente en un plazo

relativamente breve (tres a cuatro semanas) con la administración de estreptomicina.

El resultado indica la importancia de realizar un estudio analítico de los horarios actuales de la estreptomicinoterapia en la tuberculosis clínica. A falta de datos adecuados parece conveniente continuar por ahora administrando la estreptomicina a plazos frecuentes en casos de tuberculosis. Sin embargo, las dosis masivas administradas de tarde en tarde son bien toleradas por los seres humanos.

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SIMULTANEOUS SAMPLES OF ALVEOLAR AIR FROM EACH LUNG AND PARTS THEREOF[1,2]

A Preliminary Report of a Method Using Bronchial Catheterization

GÖSTA BIRATH

In experiments on animals, catheterization of the trachea has long been used to obtain alveolar air. The last portion of the expiratory air has then been collected and the samples pooled in order to have an amount sufficient for analysis. In this way it has been possible to obtain reliable values. Samples of alveolar air have also been taken from the bronchi of animals (Kramer and Sarre, 1936).

Loewy and Schrötter (1905) carried out catheterization of human bronchi with silver tubes *via* bronchoscope. By means of a rubber cuff that could be inflated around the distal end of the catheter the bronchus was entirely cut off from communication with the outside air. The samples of air that were obtained from the part of the lung cut off from the outside air were in a state of tension equilibrium with the blood gases in the venous system. Such samples had no connection—as is otherwise the case with samples of alveolar air—with the free gas exchange in the lungs. The authors found it worthy of note *wie tolerant sich die Schleimhaut der Bronchien gegenüber eingeführten Instrumenten erwies.*

Bezançon, Braun, Soulas, Guillaumin and Cachin (1936) made use of a similar arrangement involving the cutting off of one of the main bronchi, but allowing free respiration through the catheter, and collected expiratory air for examination. In this way they determined ventilation, carbon dioxide excretion and oxygen consumption from each lung separately; but this method is inferior to the bronchospirometry worked out by Björkman (1934), in which the same values were registered spirometrically. The examination of alveolar air from each lung separately has not, as far as I have been able to find, been carried out on man before.

The principle of the method here described is that, through a fine catheter passed down into the bronchial tree, a small part of the last expiratory air is removed by careful suction from a receptacle filled with mercury under ordinary respiration. The small amount of air that is obtained in this way on every respiration is repeatedly collected in the receptacle until the amount suffices for analysis.

The essential conditions that must be fulfilled if representative alveolar air samples are to be obtained are in the main as follows:

(*1*) The catheter introduced must not block the bronchial lumen and it must narrow its lumen as little as possible. With marked narrowing, ventilation in the part of the lung concerned will be impaired as it is in bronchostenosis, and the values of the gaseous composition of the alveolar air will be altered.

[1] From the Medical Tuberculosis Department of St. Göran's Hospital, Stockholm, Sweden.

[2] This study was made under a grant from the Swedish National Union against Tuberculosis.

(2) The amount of air that is removed at the end of each expiration must not be too great and it must not be aspirated too rapidly. Otherwise, one risks aspirating respiratory air from other bronchi.

(3) The respiration throughout the examination should not be so affected that the alveolar air is changed in composition (for example by hyperventilation).

(4) The ventilation in the lung examined must not be reduced beyond the point at which alveolar air, during the last part of the expiration, streams through the bronchus in which the catheter is placed.

The catheters used have been the ordinary contrast-bearing ureteral catheters, numbers 5 to 7, which are suitable both in length and diameter. The narrowest, number 5, have been provided with an extra perforation for aspirating the sample, but, nevertheless, they easily stick by suction to the bronchial wall. One advantage of these catheters is that they are graduated, so that one always knows how far they have been introduced. After each examination the catheters were sterilized—after mechanical cleaning—by immersing them for thirty minutes in a 5 per cent chloramine solution.

PROCEDURE

The mucous membranes of the nose and pharynx are anesthetized and a few drops of the anesthetic (2 per cent decicain) are injected into the bronchi. The catheters are then introduced through the nostrils. They are held in the pharynx and led into the larynx. In general, the catheter introduced through the right nasal passage runs into the left main bronchus and *vice versa*. When the catheter is introduced about 25 cm., it is at the carina, and it is only after this that one can count on its having entered one of the main bronchi. By fluoroscopy or eventually X-ray photography, one must ascertain the exact position of the catheters. If irritation provokes cough, a further small amount of the anesthetic may be injected through the catheter. When the catheters are in the desired position they are fixed with adhesive plaster to the nostrils.

One begins to take samples after the patient has been allowed to rest for five to ten minutes, or possibly longer, following the roentgen examination. At first, a small amount of air is aspirated in order to rinse the "dead space" of the apparatus (chiefly the catheter). This amount of air, like the definitive sample, is obtained by means of quick turns of the tap of the receptacle, so that only a small part of the last portion of the expiratory air is aspirated. With this procedure it is possible, without difficulty, during quiet respiration, to obtain the sample from the last third or fourth part of the expiratory air.

DISCUSSION

Under normal conditions one may expect that the air remaining in the bronchi at the end of inspiration is completely washed out during the last third of expiration. One may thus rely upon the sample's consisting of pure alveolar air; but it is not equally certain that this will be the case under pathological conditions, for if the tidal air is considerably decreased, the respiratory "dead space" will be

relatively larger as compared to the tidal air. It will, then, be no longer possible to assume that the last part of the expiratory air, even in the bronchi, will consist of pure alveolar air. This is so in spite of the fact that the size of the "dead space" is normally very small in relation to the expired alveolar air, when the sample is taken in the bronchi. Under certain conditions the respiratory excursions on one side may conceivably (for example owing to marked pleural retraction, with or without pneumothorax) be so small that the stream of air in the bronchi will consist mainly of the air of the "dead space." Markedly reduced ventilation is an obstacle to the obtaining of alveolar air with the method described here.

Another possible source of error is that the examination in itself might possibly cause hyperventilation; but, as is seen from the low respiratory quotients of the examples given below, this danger seems to be relatively slight.

By placing the catheters in different positions it should be possible to draw comparisons between the two lungs and between a lower lobe and the lung as a whole. It should be possible to ascertain interesting facts concerning the physiology of respiration under pathological conditions. It also ought to be possible to use the method when, for some reason, the taking of samples of alveolar air according to the Haldane-Priestley method is not feasible.

EXAMPLES

Case R. K. had extensive tuberculous parenchymal lesions throughout the right lung as well as small cavities. There were lesions of moderate extent in the left apex. Pneumothorax treatment was started on the right side about six weeks before bronchial catheterization. The lung was then adherent at the apex but selectively collapsed in the upper part of the lower lobe, otherwise there was moderate collapse. Catheters were introduced, one into the right main bronchus and one into the trachea just above the carina. In table 1 are shown the results that were obtained on double determinations (table 1, I and II).

It is rather uncertain whether the air obtained in this case is pure alveolar air. The surprising finding of lower oxygen values and higher carbon dioxide values in the trachea than in the right main bronchus is evidently due to admixture of alveolar air from the left lung to the sample taken in the trachea. It is possible that in the right pneumothorax lung, owing to reduced respiratory excursions, the "dead space" may be larger, which might explain the difference. Another, more probable, explanation is that the exchange of gases takes place to a lesser extent, with a poorer utilization of the oxygen and reduced carbon dioxide excretion in the pneumothorax lung (cf. Leiner, 1944). A more detailed discussion of such a case will not be possible until more cases have been studied.

Case N. A. had scattered, fresh tuberculous parenchymal lesions and cavities in both lungs. Pneumothorax was induced on both sides one and two months before bronchial catheterization. The lungs were free of adhesions, with the possible exception of the right side, where pneumothorax had first been induced. In the right pleural space, a slight exudate had formed, which may have caused basal adhesions. With one catheter samples were taken from the right main bronchus and with the other one from the left lower lobe.

The samples taken from the left lower lobe showed the lowest oxygen content and the highest carbon dioxide amount (table 2). This may indicate either that the samples obtained from the right main bronchus were not really alveolar air or that the alveolar air has a different composition in different parts of the lungs.

The carbon dioxide content of the alveolar air in the left lower lobe favors the assumption of an increased sensibility of the respiratory centre to the carbon dioxide tension in the blood in cases with bilateral pneumothorax, for the carbon dioxide tension is in this case only 33 mm., that is, lower than the normal value of about 40 mm. There is reason to believe that such an increased sensibility actually exists, though further investigations into the matter are of course necessary, especially since, due to the low respiratory quotient in this case, it is possible that the carbon dioxide tension was reduced after hyperventilation during the introduction of the catheters.

TABLE 1

Bronchial catheterization of a case with right-sided induced pneumothorax

SAMPLE TAKEN FROM	EXPERIMENT	CARBON DIOXIDE	OXYGEN	RESPIRATORY QUOTIENT
		per cent	*per cent*	
Right main bronchus	I	4.14	15.55	0.77
	II	4.50	15.00	0.76
Trachea	I	4.91	14.33	0.75
	II	5.01	14.81	0.82

TABLE 2

Bronchial catheterization of a case with bilateral pneumothorax

SAMPLE TAKEN FROM	CARBON DIOXIDE	OXYGEN	RESPIRATORY QUOTIENT
	per cent	*per cent*	
Right main bronchus	4.42	14.79	0.72
Left lower lobe	4.80	14.09	0.71

SUMMARY

In order to obtain alveolar air from each lung, bronchial catheterization has been carried out with contrast-bearing ureteral catheters and under roentgenological control to insure correct placing. Alveolar air has been obtained in this way also only from the lower lobe. An account is given of 2 patients with pulmonary tuberculosis treated with pneumothorax.

SUMARIO

A fin de obtener aire alveolar de cada pulmón se llevó a cabo un cateterismo bronquial con sondas ureterales que contenian sustancias opacas, bajo fiscalización roentgenológica a fin de garantizar la colocación adecuada. También se obtuvo en la misma forma aire alveolar exclusivamente del lóbulo inferior. Preséntase una reseña de dos tuberculosos pulmonares tratados con el neumotórax.

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PULMONARY TUBERCULOSIS SIMULATING BRONCHOGENIC CARCINOMA[1]

A Report of Four Cases

ANIBAL ROBERTO VALLE AND M. LAWRENCE WHITE, JR.

Not always can an exact preoperative diagnosis of bronchogenic carcinoma be established. Differential diagnosis cannot be made on the basis of the clinical picture alone, as the symptoms and signs are common to chronic inflammation, tuberculosis and lung abscess as well as bronchogenic carcinoma. Positive diagnosis can be established by bronchoscopic biopsy in approximately 70 per cent of the cases (6, 7, 9). In most of the remaining 30 per cent a definite diagnosis can be made only after exploratory thoracotomy.

Much has been written about bronchogenic carcinoma simulating other chest diseases, but few authors have reported cases in which other chest lesions simulate bronchogenic carcinoma.

Graham and Singer (4) report 3 cases of calcified pulmonary tuberculosis; Haight and Farris (5), a case of tuberculoma; Bradshaw and Chodoff (1), a case of anthracosilicosis; Rendich and Camiel (8), 2 cases of silicosis; Freedlander and Wolpaw (3), 4 cases of chronic inflammatory disease; Brown and Biskind (2), and Singer and Tragerman (10), one case each of lipoid pneumonia, all simulating bronchogenic carcinoma. We present 4 recent cases in which the clinical diagnosis was bronchogenic carcinoma in spite of negative bronchoscopic examinations. At exploratory thoracotomy tissue for examination was removed and a diagnosis of tuberculosis returned in 3 cases, and chronic inflammation with probable healed tuberculosis in the other. These are the only 4 cases we have explored suspecting a bronchogenic carcinoma in which the suspicion was not corroborated by operative findings.

CASE REPORTS

Case 1: W. H., a 56-year-old colored male, was admitted to the University of Virginia Hospital on August 27, 1945 with a history of productive cough of several weeks' duration. The sputum was mucoid and moderate in quantity. He had had several small hemopytses and one pulmonary hemorrhage of about 200 cc. within the two weeks prior to admission. There had been no significant weight loss.

Physical examination was essentially negative except for a few râles over the right upper and middle lobes anteriorly. No lymph nodes were palpable. Roentgen studies of the chest showed an area of pneumonitis and apparent atelectasis of the lower part of the right upper lobe and the middle lobe (figure 1). Bronchograms showed a block of the right middle lobe bronchus about 2 cm. from the main bronchus. Fluoroscopic examination revealed normal diaphragmatic function. Six sputum concentrates were negative for tubercle bacilli. Because he had worked in a granary, the sputum was examined for fungi, also with negative findings. The blood count showed 3.6 million red cells and 6,900 white cells. Urinalysis revealed 6 to 10 pus cells and occasional red blood cells per high

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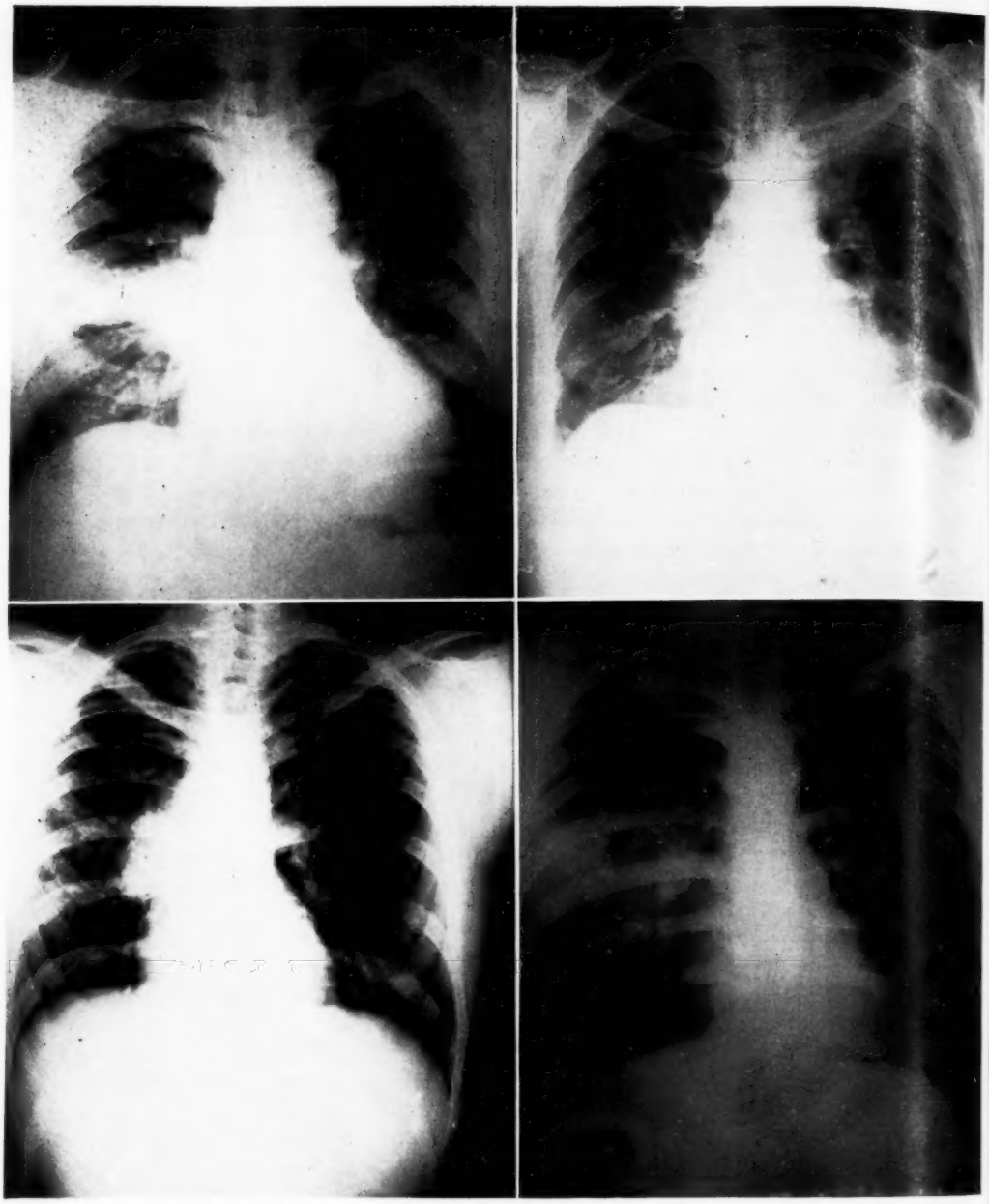

FIG. 1. (Upper left.) Case 1. A dense mass is seen extending from the hilum to the periphery of the right lung.

FIG. 2. (Upper right.) Case 2. A homogeneous area of increased density is seen in the left apex. On earlier films taken before admission this mass was seen to become progressively larger.

FIG. 3. (Lower left.) Case 3. A dense hilar mass is seen on the right with a light infiltration in the midlung zone.

FIG. 4. (Lower right.) Case 4. An area of density with central cavitation is seen in the midlung zone of the right lung.

power field. Bronchoscopic examination was negative except for the presence of blood arising both from the right upper and right middle lobe bronchi.

Operation: On September 17, 1945, through a posterolateral approach, a right exploratory thoracotomy was carried out under intratracheal nitrous oxide-ether anesthesia. The pleural cavity was entered through the periosteal bed of the resected sixth rib. No fluid was present. The upper and middle lobes were found adherent to the chest wall and were freed by blunt dissection. A hard mass, the size of an orange, involving the lower portion of the upper lobe and upper portion of the middle lobe was found. Several hard enlarged lymph nodes were found anterior and posterior to the hilum. One of these was about the size of a walnut. The hilar vessels were inaccessible and the case was considered a technically inoperable carcinoma. Several biopsies were taken, both from the mass in the lung and from the lymph nodes, and the chest was closed without drainage after 50,000 units of penicillin had been instilled in the pleural space.

Pathological report: "There are sections of three nodules. Two of these consist of well encapsulated dense hyalinized and pigmented connective tissue. The other nodule is made of dense but cellular connective tissue, in which there are ovoid-shaped zones of necrosis which are surrounded by a layer of epithelioid cells and lymphocytes. The lung sections show a slightly thickened pleura which is infiltrated with lymphocytes. The pulmonary alveoli over large areas are replaced by connective tissue, and others are filled with vacuolated monocytes. Throughout there are small tubercles, some caseous and others consisting of epithelioid cells and giant cells. These tuberculous lesions are active and appear fairly young. Although they are located in areas of old organized pneumonia, the two processes appear to be unrelated. The areas of organized pneumonia show no destruction of alveolar walls, but are organizations of intra-alveolar exudate and do not appear to be of tuberculous origin. Diagnosis: Lung showing small scattered areas of tuberculosis of miliary size, organizing nontuberculous pneumonia, caseous and calcifying tuberculous lymphadenitis." The tissue was not stained for acid-fast organisms.

The postoperative course was uneventful. The patient was transferred to a sanatorium and, at last report in November, 1945, he was doing well clinically and his roentgenograms showed improvement.

Comment: The age of the patient, his productive cough, hemoptyses and roentgenographic studies including bronchograms were indicative of bronchogenic carcinoma. The negative bronchoscopy was thought due to the fact that the lesion was beyond the range of the bronchoscope. That the vocal cords moved normally, that the diaphragm was not paralyzed and that there was no pleural fluid and no palpable peripheral lymph nodes were taken as evidence of an operable lesion. It is striking that, in spite of the repeatedly negative sputum examinations in the presence of a productive cough, the lesion was tuberculous.

Case 2: L. B., a 58-year-old white woman, was admitted to the University of Virginia Hospital on April 30, 1945. She had been well until October of 1944 when she developed a respiratory infection, characterized by a dry cough, fever and weakness. In November her cough became productive of mucopurulent sputum and small hemoptyses occurred sporadically. Wheezing was fairly constant. She had sustained a weight loss of about 40 pounds.

Physical examination revealed a decrease in breath sounds and fine moist and sibilant râles, both anteriorly and posteriorly over the left upper chest. No palpable lymph nodes were present. Laboratory data were essentially negative except for a slight anemia.

Two sputum examinations by direct smear were negative for tubercle bacilli. More examinations were not deemed necessary because of the appearance of the roentgenograms mentioned below. Three serial roentgenograms of the chest taken before admission revealed a gradually enlarging mass in the left upper lobe. The films after admission (figure 2) showed still further concentric enlargement of the density, characteristic of neoplastic growth. Fluoroscopic examination revealed normal diaphragmatic motion. Bronchoscopic examination revealed a marked displacement of the left bronchial tree toward the left; so much so, that the left upper lobe bronchus could not be well visualized. The mucosa of the left main stem bronchus was somewhat thickened and a biopsy was taken. This was negative for carcinoma and tuberculosis.

Operation: On May 4, 1945, the left chest was explored through a posterolateral approach, resecting the fifth rib. No fluid was found in the pleural space. A hard mass occupied most of the left upper lobe except for the lingula. The mass was typical of malignancy in its firmness and its apparent invasive nature. Numerous dense adhesions attached the mass to the thoracic dome. Several hard lymph nodes were palpated adjacent to the arch of the aorta and in the pulmonary ligament. After dividing the apical adhesions and mobilizing the upper lobe, the pulmonary artery was found to be surrounded by friable tissue, apparently neoplastic. The lesion was deemed inoperable and biopsies were taken from the pulmonary mass and from the lymph nodes. The chest was closed without drainage after injecting 50,000 units of penicillin into the pleural space.

Pathological report: "Scattered throughout the lung there are small tubercles; some of these are caseous and others consist only of epithelioid cells and giant cells. The pulmonary alveoli in some areas are filled with mononuclear phagocytes; other areas contain fibroblasts and others contain air. Sections from the lymph nodes contain many characteristic tubercles in all stages of development. Acid-fast stains reveal many tubercle bacilli in both the lung and the nodes. Diagnosis: Tuberculosis of lung and lymph nodes."

The patient's postoperative course was uneventful and she was discharged on the thirteenth day following operation. At last report in November, 1945, with only bed-rest as treatment, the patient was asymptomatic, had gained weight, and the roentgenographic shadow had almost disappeared.

Comment: This patient's age, the history of productive cough with small hemoptyses, the weight loss of 40 pounds, wheezing and the X-ray picture, all strongly suggested bronchogenic carcinoma. Tuberculosis was felt to have been excluded by the negative sputum examinations. Although no tumor was demonstrated at bronchoscopy, the distortion of the upper lobe bronchus was suggestive of malignancy. Even after establishing a diagnosis of tuberculosis, there was still doubt as to whether or not there was a coexisting neoplasm until the follow-up films showed almost complete regression of the lesion.

Case 3: W. B., a 29-year-old white male, was admitted to the University of Virginia Hospital on July 30, 1945, with a history of having coughed up small amounts of blood sporadically for six weeks. A mild dry cough had been present for several months and, since the hemoptyses began, he had produced small amounts of purulent sputum with the cough. There had been no weight loss, no chest pain and no wheezing. His local doctor had suspected tuberculosis, but both sputum examinations and the tuberculin test were negative. One week after the onset of the hemoptyses, he was admitted to a tuberculosis sanatorium where repeated examinations of the sputum, even by culture, were negative. These

negative findings prompted his admission to the University Hospital with a diagnosis of a pulmonary malignancy.

Physical examination in the University of Virginia Hospital disclosed a small area of dulness over the right hilar region with diminished breath sounds in this region. Fine moist râles were heard in the right midlung field. Several small, freely movable lymph nodes were palpable in the supraclavicular regions, the largest being in the left. A low grade daily fever was present. Laboratory data showed 5.1 million red cells and 8,500 white cells. Other routine examinations were noncontributory. Two sputum examinations by the concentrate method were negative for tubercle bacilli. The tuberculin test (1:1000), as well as the histoplasmin skin test, was negative. Roentgen examination showed a circumscribed mass in the right hilar region with a light infiltration in the midlung field (figure 3). The mass measured 5 x 3 cm. The left lung was clear. Fluoroscopy yielded no additional information except for visualization of a normally functioning diaphragm. Bronchoscopic examination revealed a distortion of the right bronchial tree so that the right upper lobe bronchus could not be seen. An extrinsic mass with pressure on the main stem bronchus seemed obvious. The mucosa in this area was edematous and bled easily, but no mucosal tumor was seen. The left side was normal. A supraclavicular lymph node on the left was removed and found negative for tumor specific inflammation. The findings seemed to indicate that the lesion was a malignant lymphoma, and a trial of roentgen therapy (1200 R) was given without producing any symptomatic improvement or decrease in the size of the tumor.

Operation: On August 31, 1945, through a posterolateral incision, a right exploratory thoracotomy was carried out. The sixth rib was removed subperiosteally and the pleural cavity opened. No fluid was encountered in the pleural space and the lung was not adherent to the chest wall. A mass, the size of a lemon, was palpated in the hilum of the lung. It was rock-like in consistency and so firmly fixed that removal was technically impossible. A satisfactory biopsy was taken from the mass. The chest was closed without drainage and 50,000 units of penicillin were injected into the pleural space.

Pathological report: "The section is made up of a dense, hyalinized, relatively avascular, connective tissue. In the center of this there is a small area of calcification and ossification. Diagnosis: Probably healed tuberculosis." The tissue was not stained for tubercle bacilli.

The postoperative course was uneventful and the patient was transferred to a sanatorium in the third postoperative week. At last report in November, 1945, the patient was doing well, his cough was decreasing, he had had no more hemoptyses and he was gaining weight. Roentgenograms showed the mass to have slightly decreased in size.

Comment: Although this patient was not in the cancer age, his several months' history of dry and then productive cough, the pulmonary hemorrhages and the roentgenogram strongly suggested bronchogenic or mediastinal malignancy. Because of his age and the shape and location of the mass, Hodgkin's disease received first consideration and the patient received a trial of X-ray therapy. Since no improvement resulted, an exploratory thoracotomy was indicated. Although the vocal cords and diaphragms moved normally and there was no indication of pleural fluid, the possibility of removing the lung seemed remote because of the location of the mass. This is the only case of the 4 in which the diagnosis of tuberculosis cannot be considered reasonably proved. Since tuberculosis is the commonest cause of hyalinization and calcification in lung tissue,

this must be the probable pathological diagnosis in the absence of any more specific findings.

In spite of an old, healed, apparently tuberculous mass, the pathological findings seemed to explain the patient's symptoms because of the bronchial mucosal involvement adjacent to the hilar mass. Bronchoscopy had revealed the red, easily bleeding and edematous membrane, which was the most obvious cause of the cough and hemoptyses, the two chief complaints on admission.

Case 4: F. B., a 26-year-old white male, was admitted to the University of Virginia Hospital on August 8, 1945. He had had a hacking cough for six months, but it had become productive of moderate amounts of mucoid secretions during the last two months. He also had had several small hemoptyses, a weight loss of 30 pounds, pain and wheezing in the right chest and weakness. There were vague gastro-intestinal complaints. Nine years previously he had had a small neurogenic sarcoma removed from the right flank.

Physical examination revealed fine, moist râles in the right upper chest posteriorly and anteriorly. There were no significant palpable lymph nodes. A rounded, movable mass in the right lower quadrant was presumed to be a previously diagnosed ectopic kidney. The patient was running a low grade fever. Laboratory data showed 3.7 million red cells and 9,000 white cells. The urine was normal. Nine sputum examinations by the concentrate method were negative for tubercle bacilli. Fungus cultures were negative. The intracutaneous tuberculin test was negative in concentrations of 1:10,000, 1:1,000 and 1:300. Roentgen examination showed a dense shadow with central cavitation involving the lower part of the right upper lobe and the middle lobe. The left lung was clear (figure 4). Bronchoscopy was essentially negative except for slight edema of the right main stem bronchus and the orifice of the right upper lobe.

Operation: On September 19, 1945, through a posterolateral incision, a right exploratory thoracotomy was performed. The pleural cavity was opened in the periosteal bed of the resected sixth rib. There was no pleural fluid. The right upper and middle lobes were found adherent to the chest wall. After the lung was freed, a mass, approximately 7 x 4 cm., was felt in the lower part of the upper lobe and the upper part of the middle lobe. A biopsy was taken from the mass and frozen section revealed only inflammatory tissue. The upper and middle lobes were then removed using the individual ligation technique. The five upper ribs were partially resected as an incomplete thoracoplasty and the chest was closed without drainage. Fifty thousand units of penicillin were injected into the chest daily for the first ten postoperative days and 15,000 units intramuscularly every three hours for a week, in accordance with our technique for pulmonary resection (11).

Pathological report: "The specimen consists of lung tissue apparently representing the upper and middle lobes of the right lung. In the lower portion of the upper lobe there is a large round area (8 cm.) of necrosis with central cavitation. The area is greenish-gray in color and contains diffuse small white masses, averaging 2 mm. in diameter. Sections reveal lung tissue in which there are numerous areas showing caseation. These areas are surrounded by epithelioid cells and occasional giant cells. Other sections show lung tissue with no pathological changes. Acid-fast stains of caseous areas were positive for tubercle bacilli. Diagnosis: Caseous pulmonary tuberculosis."

The postoperative course was uneventful for the first three weeks. At this time an empyema was diagnosed, believed to have been caused by tuberculosis of the bronchial stump. Since it was an infection of mixed bacterial origin, the pleural space was drained several days later. The patient was transferred to a sanatorium for further treatment. At the latest report in March, 1946, the patient was improving steadily. A thoracoplasty had been necessary to completely obliterate the mixed empyema.

Comment: Although this patient was not in the cancer age, the gradual onset of symptoms, the productive cough, the hemoptyses, the weight loss, weakness, chest pain and wheezing were suggestive of a primary malignant lesion. There was also a possibility of late metastasis from the neurogenic sarcoma which had been removed from his flank some years previously. The onset of the disease was not typical of lung abscess but it could well have represented an abscess superimposed on a malignancy. The lesion, if malignant, was felt to be probably operable. As in all doubtful cases, an exploratory operation was advised. In this case it was planned to have frozen sections made and perform a pneumonectomy if the lesion proved to be a neoplasm, and a partial resection if it were not. We did not consider the possibility of a tuberculous lesion in view of the repeated negative sputum examinations and the negative skin tests.

DISCUSSION

In the past the risk of intervention has prevented exploratory thoracotomy. Now it is justified. Hence early suspicion has become increasingly important. Delay until a definite diagnosis is made may permit an operable lesion to become inoperable either because of direct extension or distant metastasis.

In spite of modern methods, differential diagnosis is often difficult in these cases without exploration. In this series, cough, gradually becoming productive, small hemoptyses, chest pain, weight loss and weakness are all symptoms common to bronchogenic carcinoma and tuberculosis or other chronic inflammatory disease. In 3 cases of this series orthodox methods, carefully and repeatedly applied, failed to reveal tuberculosis, in spite of active lesions, both clinically and pathologically. In the fourth case pathological inactivity of the lesion makes the negative studies less surprising. The X-ray picture in all cases was suggestive of carcinoma and the bronchoscopic examinations were noncontributory.

The value of sputum examinations depends to a great extent on the ability and conscientiousness of the laboratory personnel. A report of a sputum examination negative for tubercle bacilli means little unless the previous accuracy of the technician is known. The negative examinations reported in the 4 cases were respected because of the known ability of the bacteriological technicians, the multiplicity of examinations of each patient's sputum by concentration (except in case 2), similar negative reports from a tuberculosis sanatorium in 2 of the patients and the additional evidence of negative tuberculin tests and atypical films in all 4 cases. The only tenable explanation lies in the fact that in some cases of tuberculosis it is notoriously difficult to isolate the organisms.

In exploring for possible bronchogenic carcinoma, biopsy with frozen section is useful. It must be remembered, however, that failure to obtain material from a significant portion of the diseased area may be misleading. It is generally accepted that differentiation between neoplastic and inflammatory pulmonary lesions by palpation and inspection during the exploration is at times very difficult.

Finally it should be noted that diagnostic mistakes revealed only at or after operation must be accepted if we are to make an effective attack on cancer of the lung. They can be excused only if conscientious and complete attempts at ruling

out tuberculosis have been carried out. In this connection it is also to be noted that in none of these patients was harm done by the operation and in one case a chance at surgical cure by excision of the actual lesion present was afforded.

SUMMARY

Four cases of tuberculosis simulating bronchogenic carcinoma are reported.

The difficulties of differential diagnosis are discussed.

The desirability of exploratory thoracotomy in doubtful cases is emphasized.

SUMARIO

Comunícanse cuatro casos de tuberculosis que simulaba carcinoma broncógeno.

Repásanse las dificultades que entraña el diagnóstico diferencial.

Recálcase la conveniencia de ejecutar una toracotomía exploradora en los casos dudosos.

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MITRAL STENOSIS AND PULMONARY TUBERCULOSIS[1]

ELI DAVIS[2]

Students are still taught that mitral stenosis and pulmonary tuberculosis do not occur together. White (4) reviewed the evidence and stated that the view that pulmonary tuberculosis is rare in the presence of considerable mitral stenosis appears to be true. In my experience nearly 1 per cent of patients with active pulmonary tuberculosis had mitral stenosis.

My patients with pulmonary tuberculosis have been questioned routinely for past history of rheumatic fever. Among 725 patients with active pulmonary tuberculosis and tubercle bacilli in their sputum, 27 patients gave convincing evidence of rheumatic fever, and 3 others gave a history of chorea in childhood. A history of rheumatic fever was only accepted if acute rheumatism had been diagnosed by a physician, if the age of onset was between 4 and 25 years and if the patient had had to spend at least twelve weeks in bed at the acute phase. Histories were accepted on less rigid criteria if they were supported by previous medical records, physical signs or skiagrams of the heart suggestive of rheumatic valvulitis. Of the 27 cases with evidence of rheumatic fever and tubercle bacilli in their sputum, 6 showed unequivocal signs of mitral stenosis (see table 1). In 5 of these the characteristic presystolic murmur was heard during life and, when one of these patients died, autopsy confirmed the clinical findings. The sixth patient was not known to have had mitral stenosis during life, but at autopsy presented classical rheumatic endocarditis with mitral stenosis, and phthisis. Of the remaining 21 patients, 2 more (males, aged 24 and 29) came to autopsy, but though they showed rheumatic mitral disease there was no stenosis. It is possible that other cases of mitral stenosis existed in this group but clinical proof was lacking.

TABLE 1

Six cases of mitral stenosis associated with phthisis

CASE NUMBER	SEX	AGE	AGE OF ONSET OF		REMARKS
			Rheumatic fever	Symptoms of tuberculosis	
1	F	32	11	31	Autopsy
2	M	29	No history	28	Autopsy. See text.
3	M	44	32	41	Aortic regurgitation also present.
4	F	21	7	20	
5	F	18	10	18	
6	F	28	14	27	

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During the period when these 725 patients with active tuberculosis were seen (which included the 30 cases with rheumatic fever or chorea), I saw 583 other patients with convincing histories or signs of rheumatic fever or chorea. Of these 583, 3 developed lymphocytic pleural effusions and 3 others stated that they developed active pulmonary tuberculosis from which they recovered.

SUMMARY

In several series of routine examinations of adults and school children the incidence of rheumatic heart disease was found to be approximately 1 per cent (Morris and Titmuss (1), Paul (2)). In my experience nearly 1 per cent of 725 patients with tubercle bacilli in their sputum had mitral stenosis. The incidence of rheumatic heart disease evidently exceeds that of mitral stenosis. Thus, the incidence of rheumatic heart disease in pulmonary tuberculosis would seem not to be less than that in the general population. The presence of mitral stenosis does not protect against phthisis. Roberts and Lisa (3) carefully studied the hearts of 100 patients with extensive active pulmonary tuberculosis who came to autopsy. They found healed rheumatic mitral valvulitis in 5 hearts.

SUMARIO

En varias series de exámenes sistemáticos de adultos y escolares, la incidencia de las cardiopatías reumáticas resultó ser aproximadamente de 1% (Morris y Yitmas (1), Paul (2)). En la casuística del A. casi 1% de 125 enfermos con bacilos tuberculosos en el esputo tenían estenosis mitral. La incidencia de las cardiopatías reumáticas excede manifiestamente la de la estenosis mitral, de manera que la frecuencia de las primeras en la tuberculosis pulmonar no es aparentemente menor que en la población general. La presencia de estenosis mitral no protege contra la tisis. Roberto y Lisa (3) estudiaron cuidadosamente los corazones de 100 enfermos con extensa tuberculosis pulmonar activa en quienes se hizo la autopsia, descubriendo valvulitis mitral reumática curada en cinco corazones.

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EXTRAMEDICAL SERVICES IN AN ARMY TUBERCULOSIS HOSPITAL[1]

Patient and Staff Personnel Orientation in an Army Tuberculosis Hospital

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The treatment in Army hospitals of soldiers who have developed pulmonary tuberculosis during their military service poses problems which, generically at least, resemble those found in most civilian tuberculosis hospitals. Experience with tuberculous veterans both of World War I and of World War II indicates that many are remiss in remaining under medical treatment (1). This situation is a cause of concern to Public Health Officials and others interested in the welfare of veterans and the public (2).

This report will concern itself with a discussion of techniques developed in an Army hospital, specializing in the treatment of tuberculosis, to deal with the extramedical problems commonly encountered among tuberculous soldiers.

EVALUATION OF THE PROBLEM

Ultimate rehabilitation of the tuberculous patient is dependent upon the successful integration of medical treatment, social work, vocational and educational counseling and training, and an intelligent routine for making use of leisure time.

In civilian experience the period of hospitalization is generally longer than that in an Army hospital. It has been the policy of the Army to hospitalize tuberculous soldiers until a diagnosis can be established and definitive treatment instituted (3, 4). Arrangements are then made to transfer the patient to a hospital of the Veterans Administration or a civilian hospital of the patient's choice where he may receive such additional treatment as may be required. In any case a transfer is made only when movement of the patient will not prejudice his condition. Since hospitalization in an Army hospital varies from two to six months or more, a rehabilitation program must be so designed that it is integrated into this time limitation.

Another important consideration is that federal legislation makes rehabilitation of disabled soldiers a responsibility of the Veterans Administration. Until a soldier is discharged from the service, he is not eligible to receive the benefits either of Public Law 16, 78th Congress; or Public Law 346, the Servicemen's Readjustment Act of 1944, 78th Congress.

The Army Medical Department has recognized the importance of rehabilitation of sick and wounded soldiers. Physical and Educational Reconditioning Programs have been effectively developed in Army hospitals and have contributed significantly to treatment of injuries and diseases other than tuber-

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culosis. However, the usual reconditioning techniques cannot be employed in dealing with patients with active tuberculosis.

While a variety of hospital agencies including Educational Reconditioning, American Red Cross, Occupational Therapy and others were in operation at the hospital, the knowledge of the special techniques required to deal with the problem was lacking. Moreover, such work as was being performed for the benefit of the patients was not correlated either on a service level or on the level of the individual.

The patients appeared to have the characteristic resentments concerning the Army. A majority of them had been overseas for many months and were now hospitalized in a relatively inaccessible part of the country far from home. This reaction of the patients to their disease and environment and the lack of a staff of lay personnel trained in the principles of tuberculosis treatment constituted the problem which the program to be described undertook to resolve.

GENERAL PROGRAM

Following a survey of the general situation, recommendations for a program were submitted to the Chief of Medical Service and the Commanding Officer of the hospital. The primary objective of the program was to educate the patients regarding the importance of medical treatment and to start rehabilitation which might be continued under the auspices of the Veterans Administration. For this, special orientation procedures for hospital staff personnel and the patients were developed. At the outset, participation of the various hospital services was invited on a voluntary basis.

The scheme which was approved was composed of three parts: Patient Attitude Studies, Indoctrination of Hospital Staff Personnel and Orientation of Patients. A fourth part, the Experimental Project, was added later.

1. *Patient attitude studies:* Surveys of patients' attitudes and interests were conducted as part of both the general and experimental phases of the program, in order to ascertain common problems present among patients and their general reaction to the various conditions in the hospital.

The first analysis of patient attitudes was made immediately prior to the initiation of the general program in September, 1945. This study consisted of random personal interviews with the patients on the various wards. Three major problems were revealed: the desire of the patients to know more about their disease, their uncertainty about the future and their desire to be closer to home.

A study of the psychosomatic factors in tuberculosis was made independently about this time by the Medical and Neuro-Psychiatric Services (5). Among the significant personality factors revealed by this study were obsessive and compulsive drives relating to orderliness and cleanliness, independence, resentment toward authority and optimism. The study also revealed the need for an educational project for the patient. It was recommended that this be developed as a psychotherapeutic measure to permit the patients to express their aggressive drives by constructive planning for the future.

A group of 131 patients was next studied to elicit more particular information concerning their attitudes and interests.[4] At this time the patient census in the tuberculosis section of the hospital averaged 800 patients.

Of the 131 patients, the data pertaining to 39 were eliminated because of incomplete data, undiagnosed disease, or disease other than active pulmonary tuberculosis. Analysis of the information obtained from the remaining 92 patients revealed two significant factors: first, the critical need of these patients for medical and vocational orientation; second, age distribution and educational background would make a vocational training program desirable and feasible.

Patients were studied in five wards, one of which was composed of officer patients.

(*a*) *Age:* The bulk of the patients were young men. Of the 92 patients included in the study, 60 individuals (65 per cent) were in the age group of 20 to 29 years. Of the 68 enlisted patients, 48 men (70 per cent) were between 20 and 30 years. Among the 24 officer patients, 12 (50 per cent) were between 20 and 29 years.

(*b*) *Educational level:* Seventy-six patients (83 per cent) had completed grade school. This figure included 52 (81 per cent) of the enlisted men and all officers. Of significance, too, is the fact that 31 men (27 per cent) had either started or finished college education.

(*c*) *Classification of disease:* Sixty patients (65 per cent) had minimal tubercuosis, 17 (19 per cent) moderately advanced and 15 (16 per cent) far advanced disease.

(*d*) *Length of stay:* Forty patients (43 per cent) had been at this hospital longer than four months with the maximum length of stay that of one patient who had been hospitalized thirteen months.

(*e*) *Marital status and dependency:* Fifty-three patients (58 per cent) were single, 35 (38 per cent) were married, 3 were divorced and one was widowed. Among the unmarried patients, 20 (38 per cent) had from one to three dependents. Of the married patients, all had from one to four dependents.

(*f*) *Orientation requirements:* The questionnaire employed in this study included queries concerning a variety of factors related to vocational experience and plans for the future. For example, data were obtained pertaining to principal and secondary civilian occupation prior to military service; principal and secondary assignment during military service; and vocational plans for the future.

It was found that 31 patients (34 per cent) had no plans for the future. Of these, 22 patients, or 71 per cent, reported that they could not plan because of their medical condition. Seven (23 per cent) felt that they were unable to plan because of limited education and 8 (26 per cent) because of various personal problems.

Plans for the future were reported by 61 patients or 66 per cent of the enlisted patients and of the officer patients. Significantly, a positive correlation with previous training or experience was found for 74 per cent of the patients who reported that they had plans for the future. Among 26 per cent of the patients who reported plans for the future, no correlation could be discovered between the specified plans and the previous experience or training history; among 12 per cent of the group, the future plans reported were inconsistent with either previous experience, training or medical prognosis.

In evaluating the educational needs of the group, those patients whose reactions suggested recognition of their medical problem and its concomitant economic and social

[4] Acknowledgment is made of the assistance given by Mrs. Beryl L. Smith of the National Tuberculosis Association, who did the major part of interviewing the patients in this study.

implications and appeared to be prepared to follow the course of treatment outlined for them were classified as requiring "routine orientation." Such routine orientation consisted of periodic consultation and guidance. Those patients who seemed unable or unwilling to accept the implications of their disease problem were classified as requiring "considerable orientation."

It was found that 60 per cent of the patients required routine medical orientation, and 40 per cent considerable medical orientation.

With regard to vocational orientation, 40 per cent appeared to require routine assistance and 55 per cent considerable orientation.

The need for social orientation did not seem to be urgent. The data revealed that routine social orientation was indicated for 90 per cent of the patients as compared to 10 per cent who were obviously in need of considerable social orientation.

(*g*) *Reaction of patients to medical treatment and other facilities in the hospital:* The study indicated that in general the patients were satisfied with medical care. While there were some patients in each of the wards who reported dissatisfaction with their medical officer, the almost unanimous opinion in most of the wards was that the ward officers were doing everything possible for the patients. However, in two wards a number of the patients reported dissatisfaction with their medical officers. Further investigation of this reaction indicated that the opinion of these patients was influenced by the personalities of the officers rather than by an understanding of their professional ability.

There was considerable criticism of the food served in the wards, mainly in regard to preparation and serving rather than with quality. Investigation indicated that a minimum of complaints or none at all were made by the ambulatory patients who ate their meals in the hospital mess halls in which the food was prepared in the same kitchens. The fault was found to lie partially with the unappetizing manner in which the food was being served in the wards. Frequently, it was cold by the time it reached the patients. Corrective measures easily eliminated this complaint. Loss of appetite characteristic of the disease also colored the opinions of a number of patients.

The problem of diversional activities was also commented on. Many patients felt that there should be more than two motion picture shows per week in the wards. However, from both an administrative and professional standpoint it was felt that this attitude could not be accepted.

Whereas the studies to this point were concerned mainly with eliciting general information, it was felt that there was a need for a more critical study of the factors contributing to the general problem. To study these more quantitatively, surveys of patients were subsequently included in the experimental phase.

2. *Staff indoctrination:* Study of patients' attitudes and interests as well as an analysis of the administrative procedures of the hospital indicated that hospital personnel required indoctrination on how to deal with tuberculous patients. A lecture series was therefore developed to outline the methods for dealing with the special problems of tuberculous patients. Lectures included the following subjects:

(*a*) Problems of the tuberculous patient.
(*b*) Pathogenesis and treatment of tuberculosis.
(*c*) Psychology of tuberculous patients.
(*d*) Nursing problems in tuberculosis.
(*e*) Nutrition problems in tuberculosis.
(*f*) Occupational therapy for tuberculous patients.
(*g*) The Red Cross program for tuberculous patients in an Army hospital.

These lectures were presented each week to personnel selected from the various services and departments of the hospital.

A second medium for indoctrination of hospital staff was a Tuberculosis Advisory Council. This group was made up of the chiefs of the various services and departments of the hospital or their designated representatives. Meetings of the Council were held twice each month. At these sessions, the various problems were considered, procedures evaluated and program modifications made.

3. *Patient orientation:* The patient orientation program was composed of educational as well as diversional features. Since the various programs had to reach patients on strict bed-rest and some patients permitted only limited activity, it was imperative that the patient's bedside and the ward be the focus of all the program features. Conferences with individual patients, lectures and discussions which were presented to the patient group in each ward, educational motion picture films, pamphlets, the hospital radio and public address system and newspaper were employed as the media for presenting information to the patients.

The various parts of the program were coördinated by an officer assigned to the Medical Service. This centralized control of the extramedical services made it possible to have a continuous sequence of lectures and discussions in the wards and to regulate the amount of program activity in each ward depending on the type of cases.

(*a*) *Medical:* Patients undergoing treatment were found on repeated observation to lack reliable information about tuberculosis. A considerable number of the men had been admitted for treatment after their disease had been revealed by the final examination prior to being separated from the service. These soldiers, for the most part, had had no recognizable symptoms and the disclosure of their disease had a profound psychological effect upon them.

The education of patients with regard to the fundamental principles of tuberculosis, the nature of the disease and methods of treatment was a responsibility of the ward medical officers. Following his arrival at the hospital each patient was given a copy of the pamphlet *What You Should Know about Tuberculosis.* Each new patient was also seen by his medical officer shortly after admission, and the essential facts regarding his condition were explained. Periodically thereafter, patients were scheduled for conferences with their medical officer at which times any significant changes or other matters relating to the course of their disease were explained.

However, because of the variation of training, interest and personality of the various officers it was natural that there would be differences in the effectiveness of this phase of patients' education.

Recognizing this, a plan was developed whereby several medical officers were selected to lecture on the medical aspects of tuberculosis in the various wards. These officers had had considerable experience with tuberculous patients and, in addition, had the ability to explain the subject in nonmedical language. Reaction of the patients was immediate and in favor of continuing this procedure.

(*b*) *Extramedical:* The obvious needs of most patients for information and guidance to help them develop plans for the future and deal with their immediate problems necessitated a program of extramedical orientation.

The task was essentially one of adapting the services of the various extramedical hospital agencies, such as Educational Reconditioning, Red Cross, Personal Affairs and the Library, to the particular needs of tuberculous patients. The staff orientation project helped the personnel of these agencies to better understand the problems of tuberculous patients.

The patients' education project was started with a series of lectures which were given in each ward by representatives of the agencies. The purpose of the program and the services which each agency could make available to the patients were explained. Following this, a continuous program of service was scheduled on a weekly basis.

The Educational Reconditioning Service furnished counselors who interviewed the patients regarding their educational interests. Arrangements were made for patients who were interested in taking the General Educational Development Test to obtain academic credit for qualifying experience in the military service. This test helped many patients to receive diplomas from grade and high school as well as college credit.

Vocational interests of patients were studied principally by the use of the Kuder Vocational Preference Test. Patients who took this test were counseled concerning the significance of the scores they made. Furthermore, the program served to stimulate interest in the correspondence courses available from the United States Armed Forces Institute.

The needs for social work were met by hospital case workers of the staff of the American Red Cross agency at the hospital. At the outset the number of trained workers was insufficient to meet the case load. Following recommendations made to representatives of the American Red Cross, the staff was augmented. The work performed by the hospital case workers included assistance to patients in meeting personal and family problems, assistance to patients in filing of pension claims, liaison with medical staff and other extramedical agencies and the preparation of health and welfare reports for the relatives of the patients.

The activities of the Occupational Therapy Service were considerably increased so as to provide a regular schedule of ward service to the patients. Emphasis was placed on projects which would offer controlled activity of diversional interest to bed patients, furnish graded activity for bed and ambulatory patients designed to increase work tolerance and to develop latent skills in preparation for vocational training. The ward medical officers were consulted to determine the physical limitations of the patients in order to regulate the amount of activity permitted each patient.

Problems of the patients involving pay and allowances, insurance claims, awards and decorations, and a variety of other related matters were handled by the Personal Affairs Officer, the Army Ground Forces Liaison Officer and the Army Air Forces Liaison Officer.

By ward lectures, discussions and conferences, the Veterans Administration Contact officer brought to the attention of the patients information regarding the benefits to which most of them would be entitled following discharge from the Army. Provisions of Public Law 346 and Public Law 16 were explained.

Patients were encouraged to discuss complaints and recommendations with the hospital dietitians and the Mess Officer who visited the wards regularly. Lectures on nutrition were also given in the wards. This provided both the patients and the Dietetics Service with opportunities to appreciate each other's problems and contributed materially toward improving the patients' attitude with regard to food.

The facilities of the hospital library were made available to the bed patients by frequent ward visits by the librarian. Book carts were brought to the ward on a regular schedule. Catalogues of the books in the library were distributed.

(c) *Diversional program:* Provision was made for meeting recreational needs by a

special program of ward recreation. Recognizing the limitations upon activity which the treatment of tuberculosis requires, the diversional program was planned so as to include occupational therapy projects, feature length motion pictures, USO shows and ward games which were limited to activities requiring a minimum of physical effort.

These ward activities were scheduled in the office of the program coördinator so that no ward would receive more than the indicated amount of activity. Trained Red Cross Recreation workers were responsible for providing recreational features other than occupational therapy.

EXPERIMENTAL PROGRAM

While it was suspected that there was insufficient provision for integrating the services of the various hospital agencies to the needs of individual patients, no concrete evidence was available upon which recommendations for solution could be made.

Consequently, it was decided first to investigate the value of coördinating activities and services of the various hospital agencies on the basis of individual patients and then to attempt to evaluate the effect of this procedure.

Another problem which developed during December, 1945 and January, 1946 involved a modification of the disposition policy for patients. At that time it was found that accommodations for tuberculous patients in hospitals of the Veterans Administration could not be obtained in sufficient numbers to permit the transfer of patients to the extent and frequency previously possible. This, of course, meant that patients already scheduled for Veterans Administration hospitals would have to remain at this hospital for a longer period. Following this, the census of tuberculous patients at the hospital rose to an average of 950. Therefore, as part of the experimental program, provision was also made to determine whether this development adversely affected patient morale and to develop, experimentally, program techniques to offset any deterioration in morale.

1. *Organization:* The experimental project consisted of two phases: first, development of a ward coördinator system of orientation for patients; and second, a statistical study of patients' interests and attitudes. The experimental project was started in seven wards out of a total of thirty. In addition, a like number of control wards were selected. An effort was made to have the conditions in the experimental and control wards as nearly comparable as possible.

(*a*) *Ward coördinator system:* Persons were selected from three hospital agencies: Occupational Therapy, American Red Cross and Separation Counseling. Each of these persons was assigned to work in one of the seven experimental wards. They were given the title Ward Coördinator and were to integrate the needs of the individual patients with the available services of the various hospital agencies.

Prior to the initiation of this system, the ward coördinators were given a series of lectures on the purpose of the program, the nature of the medical problem, the probable questions which could be expected from the patients and the results desired from the program.

The ward coördinators were to determine the group and individual problems in the wards and were to deal with them either on the basis of their knowledge of the problems or

by requesting specialized assistance of an appropriate hospital agency. The ward coordinators were also responsible for presenting the various questionnaires to the patients.

The patients' orientation program in the experimental wards was similar to that given in the control wards and the other tuberculosis wards of the hospital. The difference was the coördination of service to the individual. In addition, in the experimental wards patients were encouraged to suggest new program features or modifications of existing procedures which they believed would be of greater help or interest to them. Participation of patients was on a voluntary basis. Each man was given the choice of participating in the various activities or of being left alone.

(*b*) *Statistical phase:* Surveys of patient attitudes and interests were made. These studies used information obtained from attitude questionnaires, an opinion questionnaire, a biographical questionnaire and a general information questionnaire.

A time limit of one month was set for completing the various phases of the experimental project. This was done for several reasons, foremost of which was the problem of personnel which became critical as a result of the Army demobilization program. It was also felt that if the experimental project had any merit, this could be determined after a trial period of one month.

The statistical data collected generally suppported the findings in the previously discussed studies.

(1) *Attitude questionnaire:* Responses of 173 patients in the control wards and 195 in the experimental wards were obtained. The patients were asked to rate their attitudes to nine questions relating essentially to morale.

Analyzing the responses, reactions of the patients were scored and classified so as to make possible comparisons among the individual wards as well as between the control and experimental wards. The questionnaire was given twice: first, just prior to the start of the project; and, a second time, at the conclusion of the project. This made it possible also to compare any differences which might reflect the influence of the experimental project.

The data collected on the first test revealed only slight variation among the mean scores computed for the experimental and control wards. On the basis of this observation it would seem that patient attitudes in the hospital were fairly consistent. Summarizing the findings, patients rated themselves as being between "neutral" and "fairly unhappy." They felt that the hospital rated between "fair" and "poor." They felt that between "a good deal" and "a fair amount" was being done for them medically; between "a good deal" and "a fair amount" was being done for them in other ways; that for the past month or two they had felt between "good" and "fair;" that at present they felt between "good" and "fair." On the average they rated their future between "good" and "fair." Their preference regarding transfer to a Veterans Administration hospital or remaining in an Army hospital ranged between "somewhat" and "don't care" and their general morale was "fair."

The data obtained from the second questionnaire revealed differences between the mean scores of each question when compared to the scores computed for the first test. In general a shift had apparently taken place both in the control and experimental wards. This shift was manifested by a drop in morale. Measuring the change quantitatively, it was found that the drop in the control wards averaged slightly more than three times that observed in the experimental wards. It could not be determined whether the results obtained in the second questionnaire represented an actual change in patients' morale or whether it was a measure of the patients' reaction to retaking a questionnaire that had previously been given. In this connection, it was observed that many patients expressed some feeling and had to be cajoled into completing the questionnaire.

Evaluating the data, it would seem that the general reaction of the patients was not at all unusual but rather normal. It is doubtful that anyone having to follow the strict regimen of treatment as is required of tuberculous patients would be happy. Nor do most people like the idea of being in a hospital. What is surprising is that the data showed the patients to be less unhappy than might have been expected. Their opinion about the medical treatment they were receiving and the other services available seemed consistent with other attitudes. It is likely that the controversy which preceded the recent reorganization of the Veterans Administration contributed to a feeling of suspicion among the men. Many were reluctant to consider further treatment in Veterans' Hospitals for this reason.

A further clue as to the actual value of the experimental project was found in evaluating the responses made to a set of questions submitted to patients on the experimental wards at the same time that the second questionnaires were given. The patients in the experimental wards were asked whether they felt that the techniques developed during the experimental project should be incorporated into the general program and continued as part of it. Eighty-three per cent of the 140 patients who responded felt that the project should be continued and incorporated into the general program. The patients were also asked whether they were personally helped by the project. Responses of 134 patients were tabulated, 61 per cent reporting that they had been helped in amounts varying from "a little" to "a good deal." Finally, they were asked whether they believed that other patients on the ward had been helped. Seventy per cent replied in the affirmative.

(2) *Opinion questionnaire:* This was concerned with eliciting the comments and ratings which patients cared to make about the various hospital services. Analysis of the data obtained revealed that the patients felt that the hospital agencies were doing a better than average job. The patients rated the services of the American Red Cross highest. Next in order were the services of Occupational Therapy, Educational Reconditioning, the Medical Staff, Personal Affairs and the Veterans Administration Contact Representative.

Comments were also made regarding food. In this connection, the general opinion was that there had been a noticeable improvement but that further improvement was desired.

It is possible that the Red Cross recreation program which included feature length motion pictures had a significant influence upon the patients which led them to rank the general Red Cross program above that of the other services.

(3) *Biographical questionnaire:* This set of questions was given to obtain data which would primarily help the ward coördinators by furnishing information basic to counseling patients.

The statistical material collected proved to be too voluminous for presentation in this report. However, it is of interest that more than half of the 115 patients who answered the questions of the biographical questionnaire indicated that they desired to prepare themselves for future vocations. Thirty-one patients wanted to take the General Educational Development Test to receive academic credit, 19 patients desired to take the Kuder Vocational Preference Test, and 29 wished to enroll in correspondence courses of the United States Armed Forces Institute. Requests for personal interviews with vocational counselors were made by 22 patients. This information is illustrative of the practical value of this questionnaire.

(4) *General information questionnaire:* This questionnaire was based primarily on the suggestions, complaints and comments which patients had made in previous inquiries. Whereas previously the questionnaires were for the most part generic, the general in-

formation questionnaire was made up of specific questions about specific things. The patients were asked to indicate their reaction by circling "yes" or "no."

The data were valuable in further evaluating the various hospital agencies. Some rather interesting reactions were revealed. For example, it was desired to find out what the patients thought about Occupational Therapy. They were asked whether they had engaged in occupational therapy projects; whether they saw the occupational therapist often enough; whether more occupational therapists were needed and whether they felt that they were receiving as much work as they desired.

Eighty-two per cent of the men reported that they were occupied with an occupational therapy project. Only 40 per cent believed that they saw the therapist often enough. The consensus of patients was that additional therapists were more urgently needed than any other class of nonmedical personnel. Furthermore, 39 per cent of all the patients indicated a desire to do more occupational therapy.

It should be pointed out that the general activity program scheduled an occupational therapist three hours per week per ward. Another factor which undoubtedly contributed to the enthusiasm of the patients for this service was the exceptional interest and devotion to duty which was characteristic of the Occupational Therapy staff at the hospital.

It is also interesting to note that in regard to the services of the American Red Cross, patients' preference was definitely in favor of the recreation staff as compared to the social work staff. This may reflect the more popular appeal of diversional activities as compared to the more limited appreciation of the rôle of the social worker.

The questionnaire also attempted to get a more quantitative evaluation of the patients' opinions regarding medical treatment and ward discipline.

The findings generally supported those obtained previously and already discussed. Eighty-two per cent of the patients felt that they saw the ward doctor often enough. Seventy-seven per cent reported that the ward doctor was personally interested in their case. Seventy-two per cent believed that their condition had been correctly diagnosed and 78 per cent felt that correct medical treatment had been prescribed for them.

Again when these reactions were analyzed by wards it was found that in some the patients generally felt that they were not receiving the attention they deserved.

With regard to ward discipline, a sizable proportion of the men expressed a desire to have their ward quieter, yet did not wish to be transferred to another ward. This attitude undoubtedly was influenced by the friendships which had developed among the patients in the various wards and a consequent reluctance to be separated from their companions.

The problem of ward discipline was generally created by a small number of recalcitrant patients in the various wards. These sometimes influenced other patients to break hospital rules and to this extent aggravated the problem.

CONCLUSIONS

The experience described in this paper, while unique because of its setting in an Army Tuberculosis Hospital, is moreover suggestive of the vast amount of work which remains to be done with the problem of education of the tuberculous patient, not alone with regards to the nature of the disease and its personal and public health implications, but also as it impinges upon his reintegration to his community environment. Basic to this problem must be acceptance of the fact that motivation of the patient cannot be predicated entirely upon the supposition that he will react to a rational presentation of facts. Rather, he must be approached through his interests in self-preservation.

Soldiers who develop tuberculosis are hospitalized and treated in an Army Hospital only until they can be transferred to a Veterans Administration Hospital or to an institution selected by the patient. For this reason and because the Veterans Administration has the legal responsibility for the medical, economic and social rehabilitation of most of these soldiers, the usual pattern of tuberculosis rehabilitation projects is not altogether applicable in the Army Tuberculosis Hospital. Instead the emphasis must be upon orientation of the patient with the object being to impress upon him the necessity for remaining under medical care until he has received the maximum benefits of treatment.

The data clearly reveal that much can be accomplished by a coördinated rehabilitation program. That the human material considered in this study is plastic is demonstrated by the preponderance of young men as well as by their educational attainments and their desire for vocational rehabilitation assistance.

Further, the experience demonstrated that the effectiveness of a program of treatment is conditional upon availability of well-trained and experienced staff personnel operating as a team.

Finally, it should be emphasized that with the Veterans Administration lies the ultimate responsibility for the formulation of a vigorous, integrated and purposeful rehabilitation program for tuberculous veterans. Without this, it is not unreasonable to anticipate again the obvious failures of the past two decades.

SUMMARY

Recognition of the problems and consequent attitudes of tuberculous patients in an Army hospital led to the development of an orientation program designed to meet their needs for information about their disease and for guidance in planning for the future.

The program consisted of four phases:

1: Patient attitude studies.
2: Indoctrination of hospital staff personnel.
3: Orientation of patients.
4: Experimental project.

Analysis of the various data indicates that much can be done for the tuberculous soldier while he is in an Army hospital. He can be helped to understand the problems associated with his disease and his consequent responsibilities

SUMARIO

El reconocimiento de los problemas que confrontan a los tuberculosos en un hospital militar y la consiguiente actitud tomada por ellos condujo a la elaboración de una obra de orientación destinada a atender a sus necesidades de información relativa a su enfermedad y de orientación en sus planes para el futuro.

La obra comprendió cuatro fases:

1: Estudios de la actitud de los enfermos.
2: Adoctrinaciòn del personal hospitalario.
3: Orientación de los enfermos.
4: Proyecto experimental.

El análisis de los varios datos disponibles indica que cabe hacer mucho en pro del soldado tuberculoso mientras se halla en un hospital militar, pudiendo ayudársele a comprender los problemas relacionados con su enfermedad y las obligaciones que le corresponden.

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TUBERCULOSIS AND PREGNANCY[1]

EZRA BRIDGE

It is not true that pregnancy in a majority of cases has a deleterious effect on tuberculosis, neither is it true that prospective mothers with tuberculosis should be delivered by cesarean section, and it certainly is not true that all pregnancies complicated by tuberculosis should be terminated by therapeutic abortion.

What is true about the influence of pregnancy on tuberculosis cannot be shown by combining statistics from different sources. In no branch of medicine is it possible to find so many diverse opinions, each one supported by charts, figures and percentages. One author will show that mothers with tuberculosis live three times as long as unmarried women with tuberculosis. Another will prove that pregnancy is a distinct danger to married tuberculous women, and a third investigator will claim that pregnancy has no effect one way or another on a woman's tuberculosis. It would seem to be a case of "Pay your money and take your choice."

Allen K. Krause in an editorial on pregnancy and tuberculosis in the AMERICAN REVIEW OF TUBERCULOSIS (1935, *31*, 254) puts it this way: "Whether the individual inquiry approaches the problem biologically, statistically, clinically or, say, physiologically, it is at once apparent that, with few exceptions, the usual and average study proceeds from fallacious premises, gratuitous assumptions, and almost complete lack of definition and limitation of terms; and that from so unstable a foundation it limps through a morass of slip-shod data and the crudest of handling of evidence to a palpably questionable conclusion."

It would seem the problem is too complicated for simple analysis. Perhaps it will always defy solution by figures and percentages. Maybe tuberculosis in pregnancy does not change the basic reaction pattern of women to pregnancy. Maybe women who react badly to pregnancies react no differently if in addition they have tuberculosis; and, by the same token, maybe women who respond bloomingly to their pregnancies do the same if in addition they have tuberculosis.

Studies designed to clarify the problem do not incriminate shop, factory or office. Dieting as a cause cannot be blamed (women rarely starve themselves in trying to keep slender). No case can be made against insufficient clothing. Over a hundred years ago in the period of numerous petticoats and voluminous overdresses, too little clothing was even then given as a cause of so much tuberculosis. By comparison nowadays every woman should have the disease, and badly. Yet this is not so. Attempts to place the blame on smoking, late hours and strenuous sports have met without success. Even before women had the vote and before automobiles rushed hither and yon, the connection between tuberculosis and pregnancy was a problem.

Other investigations show that early marriages with child-bearing are more of a risk for tuberculous women than later marriages; that those mothers who

[1] From Iola Sanatorium, Rochester, New York.

have their children early in life have more tuberculosis than when the children come later; that mothers discovered to have tuberculosis during or after their pregnancy have a higher mortality than those who knew they had tuberculosis before they became pregnant and had adequate medical treatment. Finally, it may be stated that, if they are properly cared for, married women have no more trouble with their tuberculosis than do unmarried women.

Girls undergo a greater physiological change in becoming adults than do boys. Psychically they have greater adjustments to make; emotionally they are under greater strain particularly in the early part of their adult life. This may have some effect on the problem.

Be that as it may, experience definitely incriminates poverty, overcrowding, substandard nutrition, and poor housing as causes of high tuberculosis rates in any age and either sex.

That nature takes special care of tuberculous women during gestation has been observed for centuries. Authorities like Hippocrates, Sydenham and Rokitansky claimed that pregnancy was good for tuberculous women. This idea is not taught these days, yet all of us are impressed by the way nature seems to protect women during gestation. Many obstetricians state that a tuberculous woman rarely dies before delivery.

Given coexisting tuberculosis and pregnancy, the attitudes of the prospective parent towards the coming child need not influence the physician to any great extent. Whether a child is wanted or not is hardly the immediate concern of the physician. Most prospective mothers with tuberculosis fear that the ordeal will adversely affect their own disease, and that the infant will be born with tuberculosis.

If the pregnancy is the third one, parents should be advised to have no more children no matter what is the condition of the mother's tuberculosis. More than three pregnancies are not well borne even if the tuberculosis has been inactive for some time. Three are enough and more than three are too many.

When pregnancy becomes a reality, the mother's present and future health is of paramount importance, the father needs further educating regarding his wife's disease, and the baby deserves special consideration.

The baby will be born free of tuberculosis with a negative tuberculin reaction. It will have to be bottle fed, will be without its mother for at least six months and will be subject to tuberculosis infection and disease if the mother relaxes her pulmonary hygiene. Otherwise its chances of becoming a healthy citizen are as good as that of any infant.

The prospective father, who has aided and abetted his mate in her battle against her tuberculosis and is party of the first part, has to be advised about future pregnancies, instructed regarding the infectiousness, the chronicity and the relapsing characteristic of tuberculosis. He must be made to realize that he faces a long period when he will have full responsibility for the health and care of the baby and the mother.

The prospective mother may have minimal, moderately advanced or advanced tuberculosis. This tuberculosis may be active, inactive or the activity may be

undetermined. It may be retrogressive, slowly or rapidly progressive or stationary, and it may be predominantly exudative, fibrotic or cavernous. The extent of the tuberculosis is not so important as the status of the disease process itself. Is it active or inactive?

Ideally, the tuberculosis of a prospective mother should be arrested or inactive for at least two years. Until this is so she should be strongly advised against pregnancy. But activity itself in a tuberculous lesion is not sufficient reason to interrupt a pregnancy already started.

In general a tuberculous woman who is pregnant must have the direction and advice of a phthisiologist as well as an obstetrician. Her tuberculosis should be assiduously treated. She should have pneumothorax or phrenic interruption, if indicated, for lung relaxation. If artificial pneumothorax is indicated in the midst of a pregnancy, it should be induced; if it is being given, it should be continued. Pleural adhesions should be severed, phrenic nerve should be interrupted—all if indicated. And there should be plenty of rest, but not necessarily at this stage in a sanatorium. The regimen outlined by the obstetrician should be rigidly adhered to.

What to advise in a given case can best be presented by trimesters. If the patient seeking advice is in the first trimester she should continue with it, if her tuberculosis is inactive. If active, she must be carefully watched and especially so if there are open cavities, recent changes in her chest roentgenograms, an increase in physical signs or loss of weight or strength. Tubercle bacilli in the sputum and high sedimentation rates should not prevent continuation of a pregnancy. If the tuberculosis is rapidly progressive and the patient toxemic, interruption should be advised and the tuberculosis should have special care in a sanatorium.

If seen for the first time in the second trimester (thirteenth to twenty-eighth week) with cavernous or progressive or advanced, active tuberculosis, the pregnancy should not be interfered with; the tuberculosis should be forcibly treated. Rest should be provided, preferably in a sanatorium, artificial pneumothorax or other surgery should be used if indicated and, if possible, other control measures adopted.

If seen for the first time in the third trimester with advanced, active or progressive or cavernous tuberculosis, the pregnancy should be left alone, as induced labor sacrifices the fetus and does not benefit the mother. Here the tuberculosis needs much care and attention, including sanatorium treatment, pneumothorax if indicated, frequent X-ray examinations and close obstetrical supervision. If the tuberculosis becomes fulminating and the patient's life or the viability of the fetus is threatened, the pregnancy should be terminated by section.

Cesarean section is rarely indicated because of tuberculosis. The accepted indications, such as contracted pelvis, apply with equal force in instances where tuberculosis is present. Usually a multipara will need no help from sectioning; but a primipara in whom the head persists in riding high, and whom the obstetrician thinks will have a difficult parturition, should have the benefit of this surgical aid. Section is always indicated if the life of the infant is at stake.

Complications in the second and third trimesters, such as hemoptysis, and pleural effusion, do not indicate interruption. However, toxemia and fever of tuberculosis may occasionally have a disastrous effect on the pregnancy, thereby requiring interruption to save the infant.

Gestation itself is not dangerous to tuberculous women but delivery, puerperium and lactation are.

Birth is dangerous according to the amount of pain, mental and physical strain, and loss of blood. Birth should be under local and/or general anesthesia. Protracted dystocia must be avoided.

General anesthesia may be used with episiotomy. Ether should be avoided if possible; however, ether well administered for a short period is usually well borne. Ether badly administered may cause an irritative bronchitis. There are no contraindications to whatever analgesic or other drugs the obstetrician wishes to use, except heavy doses of morphine and atropine. Caudal anesthesia may be used if desired.

The puerperium (from end of labor to complete involution of uterus) is the dangerous period. Here the patient should be kept in bed, preferably in a sanatorium. After three weeks she may be allowed more exercise. She should have frequent chest films and special supervision by a phthisiologist. She should not nurse the infant and should not take care of it for the first half-year. She should be constantly cautioned in pulmonary hygiene.

After-care in the months to come should be directed toward her tuberculosis. Rest, adequate diet, attention to complications and frequent X-ray examinations are indicated. If asked for, advice on avoiding future pregnancies should be given.

In considering sterilization, the wishes of the wife and husband should have weight. It should be advised after the third child. It may be approved after the first or second birth when the tuberculosis is advanced, progressive or cavernous. Therapeutic interruption in the first trimester because of the severe fulminating character and the extent of the disease may be accompanied by sterilization. It should be remembered that sterilization is not a cure-all and that the mental and physical after-effects are hard to take.

A study of discharged women at Iola Sanatorium between the ages of 5 and 40 during the ten years from 1930 to 1939 showed that 97 had 152 children. At the time of their pregnancy, 9 had primary tuberculosis, 31 minimal reinfection tuberculosis, 25 moderately advanced and 22 far advanced pulmonary tuberculosis; 10 had other forms of the disease. When delivered, 55 were active and 102 inactive.

A follow-up in 1945 showed that 10 of these 97 have active tuberculosis (7 at home and 3 in the Sanatorium) and 6 have died. These figures compare favorably with results in women who have never had children.

SUMMARY

In this article an attempt has been made to show that tuberculous mothers may have children without much danger to themselves. Attitudes on therapeu-

tic abortion, cesarean section and sterilization are outlined. Details regarding care during gestation, delivery and puerperium are given.

SUMARIO

En este trabajo se ha tratado de demostrar que las madres tuberculosas pueden tener hijos sin mayor peligro para ellas. Bosquéjase la actitud tomada acerca del aborto terapéutico, la cesárea y la esterilización. También se ofrecen pormenores acerca de la asistencia que debe suministarse durante la gestación, el parto y el puerperio.

NOTICE

Annual Meeting of the American Public Health Association

October 6 to 10, 1947

The American Public Health Association announces its 75th annual meeting as taking place in Atlantic City, New Jersey, October 6 to 10, inclusive, 1947. Helping the Association to celebrate its 75th annual meeting will be the following organizations:

American School Health Association
Association of Maternal and Child Health Directors
Association of Reserve Officers of the U. S. Public Health Service
Association of State and Territorial Health Officers
Conference of Municipal Public Health Engineers
Conference of Professors of Preventive Medicine
Conference of State and Provincial Public Health Laboratory Directors
Conference of State Directors of Health Education
Conference of State Directors of Public Health Nursing
Conference of State Sanitary Engineers
National Committee of Health Council Executives
Public Health Cancer Association

Exhibits and the scientific program will point up progress in public health over a seventy-five-year span.

VETERANS HOSPITALS

A Survey That Brought Results

The New York Academy of Medicine Study of Veterans Hospitals for Tuberculosis

E. H. L. CORWIN[1]

Cognizant of the fact that after World War I one out of every 42 veterans of the military service of the United States suffered from tuberculosis to a compensable or pensionable degree, and that the service provided by the Veterans Administration was not very satisfactory, the Committee on Public Health Relations of The New York Academy of Medicine, in coöperation with the New York Tuberculosis and Health Association, carried out in 1945, under the guidance of Dr. H. McLeod Riggins, a study of the tuberculosis facilities of the Veterans Administration, with especial reference to those in New York State.

With the consent of General Frank T. Hines, then Administrator of Veterans' Affairs, a searching survey of two hospitals—one at Sunmount and the other at Castle Point, New York—was made by Dr. David Reisner as the investigator for the Committee. It was thought imperative to make such a study, in view of the expectation that large numbers of tuberculous veterans would be discharged from the armed forces of World War II. Up to January, 1945, 13,000 such veterans had been admitted to the Veterans Administration tuberculosis hospitals, of which number 17 per cent were readmissions. At the time the study was started, between 400 and 450 new patients were being admitted each month to the Veterans Hospitals.

It was also thought that the X-raying of the armed forces at the time of demobilization would add greatly to this number, since it has been estimated that from 0.3 per cent to 0.5 per cent of the total demobilized personnel would be found to have clinically significant lesions.[2] Moreover, premature return to work on the part of the veterans might result in relapses and add to the state demands on hospital facilities. It was estimated at the time that we might need to provide for about one-half a million new cases.

The study dealt with the location of the hospitals planned, medical and surgical care, administrative personnel, organization of the medical staff, vocational rehabilitation, social service, follow-up of discharged veterans and the causes of dissatisfaction among the patients. In addition to the intensive study of the two hospitals in New York State, the Committee had the advice and guidance of the following men among others who appeared at their weekly meetings: Dr. James Alexander Miller, Consulting Physician on Tuberculosis, Bellevue Hospital; Dr. J. Burns Amberson, Physician in Chief, Tuberculosis Division, Bellevue Hospital; Dr. Kendall Emerson, Managing Director, National Tuberculosis Association; Dr. Edward S. Godfrey, Commissioner of Health for New York State; Dr. Robert E. Plunkett, General Superintendent of Tuberculosis Hospitals,

[1] Executive Secretary, Committee on Public Health Relations, The New York Academy of Medicine, 2 East 103rd Street, New York 29, New York.

[2] Scattered figures, now available, would indicate that this estimate was too high and that the actual prevalence of active pulmonary tuberculosis in discharged soldiers is probably less than one in a thousand. [Editor]

New York State Department of Health; Dr. Herbert R. Edwards, Chief, Division of Tuberculosis, New York City Department of Health; Dr. Herman E. Hilleboe, then Chief, Tuberculosis Division, U. S. Public Health Service; Colonel Roy A. Wolford, Assistant Medical Director in Charge of Tuberculosis, Veterans Administration; Dr. C. W. Lester, Consulting Thoracic Surgeon, Veterans Administration Hospital, Castle Point, New York; Mr. Godias J. Drolet, Statistician, New York Tuberculosis and Health Association; and Mr. Homer Folks, Secretary, State Charities Aid Association.

The study revealed numerous inadequacies as regards service, administration and approach.

In view of a change in the Veterans Administration at the time when the report was completed, it was thought best to withhold publication temporarily. It was, however, submitted to General Bradley and General Hawley. Although many changes recommended in the report have been made with a thoroughness and rapidity which a year and a half ago would have seemed utopian, it may be of value to record the recommendations made by the Committee in July, 1945.

RECOMMENDATIONS

Recommendations with regard to social policy concerning the patient: The Joint Committee of the Committee on Public Health Relations of The New York Academy of Medicine and the New York Tuberculosis and Health Association recommended:

(*1*) That through a concerted effort on the part of the Veterans Administration, as well as the medical, nursing, social service, and rehabilitation staffs of the local hospital, the veteran and his family be educated as to the values to be gained by him and his family if he remains in the hospital until he is medically discharged. This is particularly important because a large proportion of the young veterans are in the early stage of the disease when the prospect for cure is best.

(*2*) That the Administration make an effort to place the tuberculous veteran in a hospital nearest his home which provides adequate care for his particular condition. Such a plan has the obvious advantage of treating the disabled veteran near his family and where he can keep in touch with his civilian interests.

(*3*) That veterans of World War I and World War II be properly segregated.

(*4*) That, in view of the fact that the question of disability compensation permeates the entire problem of management of the tuberculous from both the rehabilitation and public health points of view, effort be made to remedy the situation. Possibly the law should be amended to decrease the grants for home care of veterans with communicable tuberculosis who refuse hospitalization in either a Veterans Administration facility or in a suitable hospital under other auspices.

Recommendations with regard to facilities: Since the number, standards and practices of present Veterans Administration facilities are inadequate and additional provision for the World War II veteran is required, the Committee recommended:

(1) That the new tuberculous veteran be placed in a state or local sanatorium of recognized standing nearest his home at government expense.

(2) That, if this plan is not feasible in all instances, new facilities be provided in suitable locations near centres of medical activity where affiliation, consultation and exchange of training personnel can easily be arranged.

(3) That the existing Veterans Administration tuberculosis facilities be completely reorganized along recognized patterns of effective service.

Recommendations with regard to medical staff:

(1) That the medical personnel of the Veterans Administration tuberculosis facilities be set up on a corps basis, similar to that of the United States Public Health Service, and that the clinical work of the medical staff be separated from compensation and pension work and related problems, the latter to be taken care of by nonmedical personnel.

(2) That the requirements and provisions for appointments, salary, tenure of office, promotion and retirement of the medical staff, be taken out of civil service and placed under a system similar to that of the United States Public Health Service.

(3) That, if it is not possible to inaugurate the corps plan, the medical personnel be organized under a Chief Medical Officer of eminence and of proved administrative ability who shall rank as an associate administrator and report only to the Administrator; and that the Chief Medical Officer be in full charge of all medical and professional services, and also be responsible for the medical policies of the Administrator.

(4) That the Veterans Administration set up an active medical advisory board of civilian physicians to advise the national Veterans Administration.

(5) That inducements to take up the medical work in the Veterans Hospitals be based on such considerations as opportunities for (*a*) professional achievement, (*b*) advancement on clinical grounds and (*c*) research work. The promotion and compensation of medical personnel should not depend entirely upon seniority, age or office-title. Full consideration should be given to ability, achievement and initiative. In this connection the Committee would further recommend:

(6) That, after competent medical leadership has been established in the Veterans Hospitals and after these hospitals have been approved by the appropriate national bodies, a proper number of residencies be created in each facility.

(7) That there be established in the Veterans Administration a definite and generous policy of graduate education under which medical officers would be given fellowships (including tuition and regular salary) for specialized instruction; and that this policy include aid and encouragement of the medical officer in qualifying under the specialty boards. The institution of such a policy would result in great and lasting benefits to the Veterans service.

(8) That each hospital have on its staff a full-time pathologist, a roentgenolo-

gist and an adequately trained bronchoscopist who may be a member either of the medical or of the surgical staff.

(*9*) That the entire medical staff be reorganized so that the clinical director can carry out the recognized duties of this office and not be burdened by quasi-medical work; that the remaining members of the staff assume their duties and responsibilities in accordance with their titles; and that the paper work of the medical staff be assumed by a well-trained administrative staff.

(*10*) That the differentiation of duties of the members of the staff not be carried to the extent that only one of the staff is responsible for the pneumothorax work. It should be part of the work of every ward physician.

(*11*) That New York State have at least one adequate thoracic surgical centre in one of the Veterans facilities where patients from other hospitals may be transferred for major surgery. The Committee believes that in the next ten years the surgical treatment will be further emphasized but that only one centre should be organized now. The centre should have a competent full-time surgical staff with well trained assistants and an outstanding civilian medical consultant. It would be desirable if the thoracic surgeon were certified by the American Board of Surgery.

(*12*) That clinical records of all veterans be made available according to a district or a state plan.

(*13*) That outpatient departments be established by the Veterans Administration in coöperation with local health departments and local tuberculosis hospitals in the various parts of the country for the purpose of follow-up work and supervision of veterans, with particular attention to those who still have the disease in a communicable stage.

(*14*) That vocational, recreational and rehabilitative services be instituted in all Veterans facilities.

(*15*) That a comprehensive plan for medical social service be organized to humanize the institutions and to effect friendly relations between the hospital and the patient and the patient's family.

(*16*) That the work of the social service of the local hospital be integrated with the general organization of the Veterans Administration, whereby all the local welfare and health agencies, including the local Red Cross and local unit of the Veterans Administration, might work to a common end.

(*17*) That, in relation to veterans who constitute a public health menace because of tuberculosis, the public health authorities apply the same educational and police powers that are exercised to encourage or enforce hospitalization of others in the community, similarly affected.

The membership of the Joint Committee consisted of: Drs. H. McLeod Riggins, Chairman; Albert C. Herring; Chas. Gordon Heyd; Harry S. Mustard; Max Pinner; Grant Thorburn; and E. H. L. Corwin, Secretary.

TUBERCULOSIS IN DISCHARGED SOLDIERS

WILLIAM PORTER SWISHER[1]

An evaluation of the results of the first great mass X-ray survey of men inducted into the Army is now possible, since we are now in the process of reëxamining them prior to their return to civilian life. In a large percentage of cases the induction film has been available for comparison with the film taken at separation. Available statistics on the discharge rate of soldiers throughout the war because of tuberculosis are known. From review of these findings we can evaluate the success of the program, determine the sources of error and perhaps suggest ways of diminishing them, and study the effect of this program on the future public health aspects of the disease.

Each soldier at the time of discharge is given a complete physical examination and an X-ray examination of the chest. If there is any questionable shadow on the film, it is repeated and the soldier is sent to the hospital for study.

From the time the separation center started until March 15, 1946, 196,000 soldiers were examined at Separation Center Number 33, Camp McCoy, Wisconsin. Of this number, 226, or 1.15 per thousand, were sent to the hospital for further study in regard to tuberculosis. No disease was found in 24 and in 20 a diagnosis of arrested tuberculosis was made; 175, or 0.88 per thousand, were diagnosed as having active tuberculosis. Rates were somewhat higher than seen in other separation centers in the Sixth Service Command. However, these low figures are in contrast to the 3 to 15 per thousand as found in the same age group on induction (2, 8, 11, 22) and the 6 per thousand found in civilian industrial surveys (7, 19). This indicates that there is considerably less tuberculosis in the Army than in the rest of the population. It is also an index of the success of the program for screening at induction by the use of chest films.

The records of the first 157 consecutive cases of tuberculosis admitted to the hospital were studied (see table 1). It was found that 73 per cent gave no evidence of tuberculosis on physical examination. Bobrowitz (1) in a similar survey found a percentage of 71 and Morse (11) in a survey of minimal tuberculosis found that 86 per cent showed no physical signs. Until 1940 a history and physical examination was the method generally used for screening out active tuberculosis.

Further study of these cases revealed that 47 per cent had minimal tuberculosis, 40 per cent were moderately advanced and 7 per cent were far advanced; 6 per cent were not classified; 10 of the far advanced cases had more than one lobe involved, including one patient with miliary tuberculosis. All patients with far advanced lesions had elevated sedimentation rates and afternoon temperatures above 99°F.

There were 62 patients with moderately advanced tuberculosis. If routine X-ray examination of the chest had been omitted 64 per cent of these moderately advanced cases would have been missed. Of the 74 minimal cases, 52, or 70

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per cent, had neither physical findings nor a pertinent history, further emphasizing the importance of the routine X-ray films in finding minimal tuberculosis.

The location of the lesion, as shown in the flat film, was studied (see table 2). In the minimal cases the lesion was found in the same proportion in either lung. In the moderately advanced cases it was most frequently seen in the right upper lung field and the second most frequent location was the upper left lung field. The higher incidence of disease in the right upper lung field in this small series of moderately advanced cases is in keeping with the observations of others in larger series (18).

TABLE 1

Percentage of patients without symptoms or physical findings

	MINIMAL	MODERATELY ADVANCED	FAR ADVANCED	NOT CLASSIFIED	TOTAL
Without symptoms	87	80	46	80	80
Without physical findings	80	76	28	60	73
Without symptoms or physical findings	70	64	0	50	58

TABLE 2

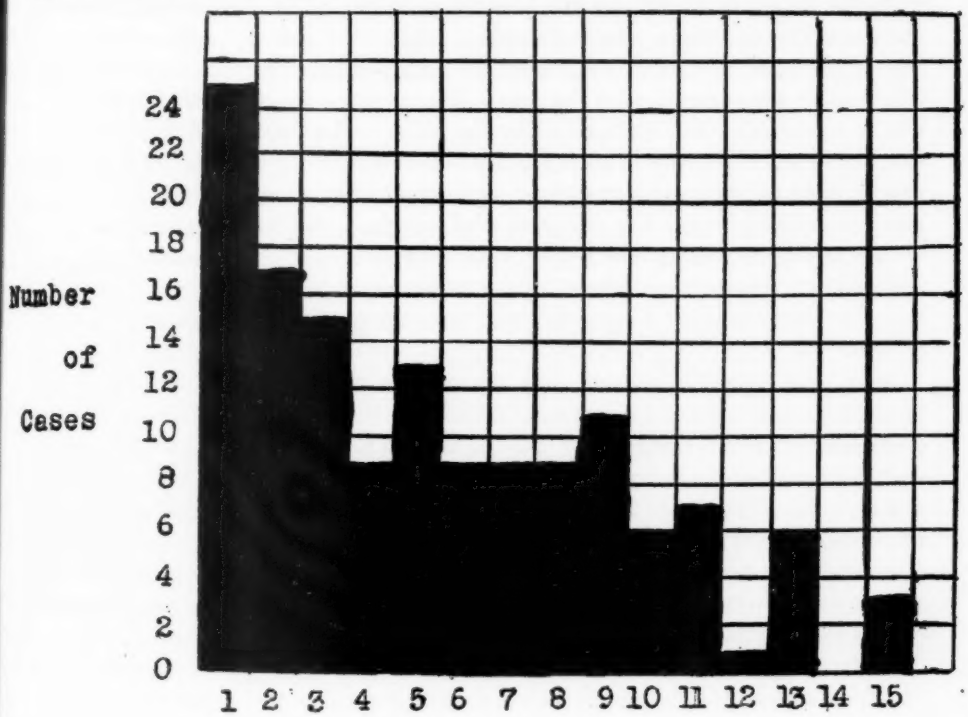
Portion of lung field involved in minimal and moderately advanced cases

	RIGHT LUNG FIELD			LEFT LUNG FIELD		
	Upper Third	Middle Third	Lower Third	Upper Third	Middle Third	Lower Third
Minimal	30	7	0	29	6	0
Moderately advanced	32	5	0	25	0	0

Gastric washings were used if the patients could not readily raise sputum. Smears of the concentrates of these washings were examined daily on twelve consecutive mornings. While this may not have been the ideal method and the possibility of some false positive findings existed, facilities for injecting such a large number of guinea pigs were not available. Cultures were made in most instances if acid-fast bacilli were seen on smears. The laboratory workers were diligent and interested in the problem and contributed greatly to the success of this method of demonstrating acid-fast bacilli. If the process had been stopped after the third examination, 56 per cent of the cases would have been missed (see graph 1). When we study only the minimal cases, 32 per cent had positive smears during the first three examinations and 68 per cent would have been missed if twelve daily gastric washings had not been examined. More positive cases would have been discovered had animal inoculation been used in addition to examining the smear (4, 12, 15).

When the separation center opened, we had a number of patients in whom we could not demonstrate acid-fast bacilli in the gastric washing in spite of unequivocal X-ray evidence of pulmonary disease. This was due to some errors in the concentration technique which were eliminated in October, 1945.

There was no correlation between the character of the density as shown on X-ray films, the number of times gastric washings were examined before acid-fast bacilli were found, the sedimentation rate rise or the elevation of afternoon



GRAPH 1

temperature. This correlation was sought in an attempt to arrive at some means of determining activity with greater ease.

Induction films were available on 62 of the patients with proved active tuberculosis. Twenty-nine, or approximately one-half of these films, showed tuberculosis lesions which could be seen without difficulty. Another 12 had changes which were equivocal due either to the film technique or the nature of the lesion. Captain Stearns found that 66 out of 100 soldiers hospitalized because of tuberculosis had shadows on their induction films that should have been investigated at that time (5). It is unwise to assume from these small surveys that if every induction film had been read accurately our tuberculosis rate at separation cen-

ters would have been cut in half. On the other hand, the problem of the "missed" case on induction has been a source of concern for some time. Long and Stearns (9), in reviewing induction films, found an average of 6 cases of tuberculosis per ten thousand films studied. They listed as causes for these errors: unskilled roentgenologists, the obscuring of minimal lesions by bony structures, clerical errors and the monotony and fatigue caused by this type of work. Attempts were made to improve the roentgenological survey and to eliminate the source of error. As any procedure is only as good as the men who do the work, it seems to be a logical starting point. Extremely rapid expansion of the Army found it with an insufficient number of adequately trained men to read the films in the early days of the war. However, since many of our cases had rather obvious lesions on induction, the factor of fatigue must be considered. For example, laboratory workers in studying smears for acid-fast bacilli have been known to finish their work quickly finding all smears negative, but when a positive smear is found this stimulates interest and the technicians spend more time studying the slides resulting in more positive smears. It is the spark of interest that results in efficient work. The roentgenologist must be imbued with the importance and significance of his work in any mass studies in order to minimize errors.

Roentgenological techniques also have been stressed in the literature and their importance cannot be overemphasized. Better visualization of the lung fields leads to less fatigue to the interpreter and better end-results. The stereoscopic view plus the examination of each film separarely should give optimum results (15). The 4 x 5″ film, according to those who have studied comparative methods, results in a minimum of expense and a minimum of lesions missed because of the technique (6, 10, 13, 22). In our experience the induction films that were full-sized had as high a percentage of missed lesions as the smaller ones, showing that the "fatigue" element was the important factor.

Perhaps by choosing the proper type of roentgenologist for this work we can pick one who likes routine and has a definite feeling of satisfaction for exacting detail. In order to select men who have exceptional capacity for reading many films for prolonged periods of time, some test may be devised. One rather simple test to determine a man's aptitude would be occasionally to insert a certain known number of positive chest films in the daily routine. This would, after standardization, give any film reader his percentage error. It could be repeated from time to time as a check on the individual. In a short time there would be a large group of radiologists who could read a large number of X-ray films daily and the percentage of errors could be kept at a definite known level at all times.

Another suggestion to add to the preventative measures taken by the United States Army would be a method of "follow-up" in indicated cases. It is generally believed that persons with preëxisting arrested or healed tuberculosis are more susceptible to reactivation of the disease under stress, especially in the younger age group. Such persons would do well to have a chest film every three to six months, depending on their condition. Others who need closer supervision are

those who give a history of tuberculosis in the family, the case with pleurisy with effusion of unknown etiology, the patient with spontaneous pneumothorax and perhaps even the person with a negative tuberculin test (4, 20). A tuberculosis register could be instituted similar to the syphilis register in the soldier's service record. In this way the suspect would get a chest film at needed intervals. This would provide as effective a follow-up on tuberculosis suspects as it does in the syphilitic.

A central committee of qualified men would provide a standard interpretation of the films and a central clearing house for the films which would be readily available if the individual's progress indicated the need for further study in a general hospital.

The routine use of the chest X-ray film in the Army has been one of the greatest contributions to case-finding and treatment of tuberculosis in recent years and a tremendously effective public health measure. It is perhaps the forerunner of an era when everyone will have a periodic chest film, just as to-day many have periodic urinalysis and serological tests. By these means pulmonary tuberculosis will be found in the minimal stage and clinics, hospitals and sanatoria will be treating mainly minimal cases with resulting shorter periods of hospitalization and better prognosis (17, 20).

SUMMARY

A study of tuberculosis patients, as revealed by the Camp McCoy Wisconsin Separation Center Number 33, revealed that, in 196,000 soldiers, active tuberculosis was found in 0.88 per thousand; 62 per cent of these had neither a history of symptoms nor signs on physical examination that would have led to the diagnosis; 47 per cent had minimal tuberculosis; 40 per cent were moderately advanced; 7 per cent were far advanced and 6 per cent were not classified. The lesion was usually located in the upper third of the lung fields and lesions in the right upper lung field were more frequent than in the left upper lung field.

The value of repeated examinations of the gastric washings for acid-fast bacilli was evident; only 44 per cent of the cases had positive smears on the first three examinations.

Approximately one-half of the induction films available of these patients showed tuberculous lesions. These errors in reading induction films are discussed and a method of keeping them at a minimum is presented.

A method of closer follow-up is suggested by which arested and suspicious cases would get interval chest films. The universal use of X-ray examination as a method for screening out tuberculosis opens the possibility for the elimination of the disease.

SUMARIO

Tuberculosis en Los Licenciados del Ejército

A la luz de los datos del centro de Separación No. 33 en el Campamento McCoy de Wisconsin, de 196,000 soldados separados del Ejército de E. U. A., 0.88

por ciento revelaron tuberculosis activa; en 62 por ciento de ellos no había antecedentes de síntomas o signos descubiertos por el examen físico que hubieran orientado el diagnóstico; 47 por ciento tenían tuberculosis mínima; 40 por ciento moderadamente avanzada; 7 por ciento muy avanzada; y 6 por ciento no fueron clasificados. Por lo general la lesión se hallaba en el tercio superior de los campos pulmonares, siendo más frecuentes en el lado derecho que en el izquierdo.

Resultó manifiesto el valor de los exámenes repetidos de los lavados gástricos en busca de bacilos ácidorresistentes; sólo 44 por ciento de los casos mostraron frotes positivos en los primeros tres exámenes.

Aproximadamente la mitad de las películas de entrada que había para estos enfermos revelaban lesiones tuberculosas. Discútense estos errores en la lectura de las peliculas de ingreso, ofreciéndose un método para reducirlos al mínimo.

Propónese un método para observación subsecuente más detenida, con el cual se harían periódicamente películas torácicas en los casos estacionados y sospechosos. El empleo universal de los exámenes roentgenológicos para despistar la tuberculosis entreabre la posibilidad de eliminar la enfermedad.

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THE QUANTITATIVE TUBERCULIN TEST[1,2]

Its Significance in the Diagnosis of Tuberculosis

C. EUGENE WOODRUFF

Recent developments in the antituberculosis compaign have considerably increased the burden of the sanatorium laboratory. Fifteen years ago, for example, nearly all of the patients admitted to Maybury Sanatorium were either referred by another hospital or by some physician to whom the patient had gone because of symptoms. By way of contrast, the present day roster of admissions shows occasional patients picked up by a preëmployment X-ray examination or in some group survey and sent to the Sanatorium solely because of a suspicious shadow in the X-ray film. Under such conditions, with an increased proportion of patients hospitalized because of X-ray findings alone instead of X-ray findings *plus symptoms*, there is a disproportionate increase in the number of cases of sarcoidosis, bronchiectasis, atypical pneumonia and lung abscess which, so to speak, have been filtered out by the X-ray screen. It is the responsibility of the laboratory to pass final judgment regarding the correctness of the diagnosis in each such case. It is because of the weight of this responsibility that the present plea is made for a more effective use of that old tool, the tuberculin test.

During the past five years, 3,381 patients, either newly admitted or readmitted to the Wm. Maybury Sanatorium, have been tested with tuberculin. These patients varied in age from 13 to 80 years. The tests were given intracutaneously, using 0.1 ml. of a 1:10,000 dilution of OT (0.01 mg.). They were given routinely by the technologist, after she had taken the patient's blood count. The same lot of OT, diluted as needed, was used throughout the study. Old Tuberculin[3] was employed rather than tuberculin PPD, first because it was more readily available and second in order that the results of this study might be more closely comparable with those of other studies in this area.

Reactions were read at the end of forty-eight hours; an area of induration or edema 5 mm. or more in diameter was considered a positive reaction. Patients negative to the first dilution were tested with 1:1000 OT and, if still negative, were retested at forty-eight-hour intervals thereafter with tuberculin ten times as concentrated. The final dilution used was 1:10 OT (10 mg.). In subsequent portions of the paper those patients who failed to react to the 1:10 dilution of tuberculin are referred to as *anergic* patients.

There was some variation in procedure with regard to the tuberculin tests over the five-year period. During the earlier years an interval of a few days to as much as two weeks elapsed after the first tuberculin test before the negative reactors were tested with more concentrated tuberculin. During the past year,

[1] Presented in part before the meeting of the Michigan Trudeau Society, Detroit, Michigan, November 7, 1946.

[2] From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

[3] Furnished by Parke, Davis and Company, Detroit, Michigan.

on the other hand, the repeated tuberculin tests have been run immediately, in most cases, after the preceding test was read as negative.

Distribution of the total number of patients according to sensitivity to tuberculin is shown in table 1.

In a large series of patients, then, who are hospitalized either because of proved tuberculosis or because of X-ray findings suggestive of tuberculosis one may expect to find well over 90 per cent showing a positive reaction to either the 1:10,000 or the 1:1000 dilution of OT. If the tests are continued, one will find a small number of patients who fail to react to even the 1:10 dilution of tuberculin. In the present study that number was 43, or 1.3 per cent. This number compares with 2.3 per cent found negative to the 1:10 dilution of tuberculin by Musacchio (1) when he tested 1,000 patients at the Herman Kiefer Hospital in Detroit. The reason for this discrepancy is to be found in the 90 patients listed in table 1 as negative to 1:10,000 OT. Most of these 90 patients were accumulated during the first three or four years of the present study when there was considerable delay before the tests with more concentrated tuberculin were given. Undoubtedly, many of the 90 would have been found negative to the 1:10 dilution of tuberculin had their tests been run more expeditiously, for among the group were 56 patients who died before they had received any test other than the initial one.

TABLE 1

Distribution of patients according to tuberculin sensitivity

	NUMBER	OBSERVED	ADJUSTED
		per cent	*per cent*
Positive 1:10,000	2,699	79.8	79.8
Positive 1:1,000	452	13.4	14.0
Positive 1:100	55	1.6	1.8
Negative 1:10,000	90	2.7	
Negative 1:100	42	1.2	1.5
Negative 1:10	43	1.3	2.9
Total	3,381	100.0	100.0

During the past year, as already mentioned, the tests with more concentrated tuberculin have been given immediately, in most cases, after the preceding test was read as negative. Among the 758 patients tested in this manner, 22, or 2.9 per cent, have been found who failed to react to 1:10 OT. Considering these facts a reallocation of the patients listed merely as "negative to 1:10,000" would bring the total number of patients negative to 1:10 OT at least to the 2.3 per cent found by Musacchio, more probably to around 3 per cent of the total. In the column labelled "Adjusted Per Cent" such a reallocation has been attempted on the basis of our experience with the 758 patients.

The 43 anergic patients of the present study are classified according to diagnosis in table 2. Note that the fatality was 100 per cent among the 15 patients

who had pulmonary tuberculosis. All 15 were critically ill when admitted to the Sanatorium; all were dead in less than six weeks after their admission.

There were no other fatalities in the anergic group. The patient with Friedlander's pneumonia, though critically ill on admission, has improved, and should be ready for discharge soon. The patient with Pott's disease should also be ready for an early discharge. All of the remaining 26 patients have been discharged. Twenty-three were considered nontuberculous, or at least without active tuberculosis. Three of the patients with tracheobronchial lymphadenitis developed positive reactions to the 1:1000 dilution of tuberculin in less than three months after their admission to the Sanatorium. One can only speculate as to whether these 3 had primary infections when admitted, and had not yet become allergic, or whether they picked up primary infections while in the San-

TABLE 2

Anergic patients classified according to diagnosis

DIAGNOSIS	NUMBER OF CASES		PRESENT CONDITION		
	Total	Acutely ill on admission	Dead	Discharged	Active
Pulmonary tuberculosis	15	15	15	0	0
Tracheobronchial lymphadenitis	9	0	0	9	0
Atypical pneumonia	6	0	0	6	0
Sarcoidosis	6	0	0	6	0
Bronchiectasis	3	0	0	3	0
Pulmonary fibrosis	2	0	0	2	0
Pott's disease	1	0	0	0	1
Friedlander's pneumonia	1	1	0	0	1
Total	43	16	15	26	2

atorium. The patient with Friedlander's pneumonia became allergic with the improvement in his condition. The patient with Pott's disease also developed allergy within three months of his hospital admission.

Tubercle bacilli were found in the sputum of all 15 of the anergic patients who had pulmonary tuberculosis. In 13 instances the bacilli were present in large numbers in direct smears of the sputum. The other 2 patients, who had miliary disease, showed tubercle bacilli only when the sputum was cultured. Also, the patient with Friedlander's bacillus infection had a positive sputum culture on admission. Since then, with the improvement in his condition, he has had 2 negative sputum cultures and a guinea pig inoculation which proved to be negative. Tubercle bacilli were not recovered from any of the remaining anergic patients, in spite of a total of 171 examinations of sputum smears, 39 sputum cultures and 7 cultures of gastric washings.

VALUE OF THE TUBERCULIN TEST

A tuberculin survey made in Detroit in 1937 and 1938 (2), involving more than 100,000 tuberculin tests, revealed 31,592 reactors, but clinical tuberculosis

was found in only about 2 per cent of these reactors. Similar results have been obtained in many other American studies, including those in Minneapolis (3). Since the tuberculin test reveals such a small number of cases of clinical tuberculosis it is rarely used at present as the primary agent in a case-finding survey. However, this fact does not in the least minimize the importance of testing with tuberculin those persons who have been found by the X-ray examination to have suspicious pulmonary shadows. In this group the tuberculin test is of the greatest value as corroborative evidence for or against the diagnosis of tuberculosis. It is of particular importance in those patients who fail to show tubercle bacilli in smears of the sputum, for the results of the tuberculin test are available long before any answer can be expected from cultures of sputum or gastric contents.

In the present study, 93.2 per cent of the newly admitted patients were observed to react to either the 1:10,000 or the 1:1,000 dilution of tuberculin. If one considered only cases of minimal disease, where the diagnostic problem is frequently most difficult, the percentage of positive reactors would be well over 95.

The tuberculin testing of patients cannot be considered complete unless those who fail to react to the initial dose are tested with successively stronger concentrations of OT to determine quantitatively their level of tuberculin sensitivity. If, finally, a patient fails to react to the 1:10 dilution of tuberculin, certain rules are helpful in making a diagnosis. As was stated some years ago by Douglas (2) "... there is little evidence to indicate that persons with really active tuberculous disease of either primary or reinfection type fail to react to tuberculin, except in well known circumstances, such as during certain acute communicable diseases, terminal stages of or very acute forms of tuberculosis itself, the later weeks of pregnancy and following certain severe surgical operations...." Paraphrasing this statement for the present study one may say that the person in good general condition, who has a lesion suggestive of pulmonary tuberculosis, should also show a positive reaction to 1:10,000 or 1:1,000 OT before the diagnosis is confirmed. Further, one may say that a patient anergic to tuberculin, who is not acutely ill, almost certainly does not have clinical tuberculosis.

The anergic patient with active pulmonary tuberculosis is always close to death, as was evidenced by the 100 per cent fatality of such patients in the present series. In a small series of 54 tuberculous patients (4) whose sensitivity level was determined shortly before death, 14, or 26 per cent, were found to be anergic.

If the anergic tuberculous patient is producing sputum the diagnosis should be made easy by the finding of great numbers of tubercle bacilli. A reason for the large numbers of tubercle bacilli in the sputum of the anergic patient has been suggested by Brosius (5) who found that tubercle bacilli grow not only in pulmonary cavities but throughout the lung tissues of the anergic patient. Bogen and Bennett (6) showed that the fatality rate is much higher in patients with numerous tubercle bacilli in the sputum than in those who are excreting very few tubercle bacilli. Finally, the careful study of Furcolow and coworkers

(7) has indicated the higher fatality rate among tuberculous patients with a low level of sensitivity to tuberculin.

The quantitative tuberculin tests have not only aided in solving occasional bizarre diagnostic problems, but have made possible the detection of those rare errors which may creep into the reports of even the best ordered laboratory. For example, a positive sputum culture was reported in the case of a healthy *anergic* person. Because this patient was anergic the culture was checked immediately by animal inoculation; no disease resulted in the guinea pig. This is but one of several instances in which costly errors have been avoided or corrected because of the tuberculin test. The knowledge that tubercle bacilli are not found in the sputum of an anergic patient unless he is critically ill gives an effective check on the most important of all laboratory reports—that regarding the sputum.

DISCUSSION

A recent editorial in Public Health Reports (8) emphasized the need for checking X-ray findings with the tuberculin test before a definite diagnosis of tuberculosis is made. With this we can agree whole-heartedly. In the hospitalized patient with minimal or moderately advanced disease, who does not appear critically ill, the finding of either a positive tuberculin reaction or of tubercle bacilli in the sputum or gastric washings should be considered imperative before tuberculosis is diagnosed.

While agreeing to this extent with the editorial (8) one must take exception to the statement, "In the presence of a negative tuberculin test other reasons than tuberculosis must be found for suspicious shadows, even though their location or conformation be characteristic." This statement ignores the group of tuberculous patients who are anergic because of their extensive disease. Though small, this group is important, since it contains the patients most likely to be excreting large numbers of tubercle bacilli in the sputum.

From the experience gathered during the past five years the Clinical Staff of the Maybury Sanatorium is convinced of the diagnostic value of the quantitative tuberculin test. We believe that a tuberculin test should be given routinely to every patient when he is first admitted to the Sanatorium. Only in that way will the results be available at the time they are most needed—when initial therapeutic measures are being considered.

If the patient fails to react to the 1:10,000 dilution of tuberculin he should receive successively stronger concentrations to determine as accurately as possible his level of tuberculin sensitivity. If he proves to be anergic to tuberculin, the diagnosis is simplified by the use of two rules which have proved true without exception in our experience: (*1*) the anergic tuberculous patient is much more likely to have large numbers of tubercle bacilli in his sputum than is the highly allergic patient; (*2*) the anergic patient with active pulmonary tuberculosis is always acutely ill. A corollary of this last rule is that tubercle bacilli are never found in the sputum of an anergic patient unless he is acutely ill.

The above two rules and their corollary enable one to approach the differential

diagnosis of the anergic patient with confidence. In fact such a diagnosis can usually be made by merely answering the question, "Is the patient critically ill, or is he not?" While anergic patients with pneumococcus pneumonia may be very ill, diagnostic problems of this type rarely reach the tuberculosis sanatorium, being excluded by the characteristic X-ray picture and the other signs and symptoms. The highly allergic tuberculous patient may or may not appear ill; the anergic tuberculous patient is always very ill.

A brief experience with the carefully executed and properly interpreted quantitative tuberculin test will convince one that it is a most useful tool for the differential diagnosis of pulmonary lesions.

SUMMARY

1. The patient in relatively good general condition who is suspected of having tuberculosis should exhibit a positive tuberculin reaction in confirmation of the diagnosis.

2. In any large series of patients with roentgenograms suggestive of tuberculosis a certain number will be encountered who fail to react to tuberculin in high concentration. The differential diagnosis in such cases is simplified by the knowledge that the patient with active pulmonary tuberculosis who is anergic is always critically ill. Any anergic patient who does not appear ill is probably nontuberculous, regardless of the X-ray findings.

3. Tubercle bacilli are never found in the sputum of an anergic patient unless he is critically ill.

4. The anergic tuberculous patient is much more likely to have large numbers of tubercle bacilli in his sputum than is the highly allergic patient.

5. Routine tuberculin tests are one of the most important contributions of the laboratory to the diagnosis of tuberculosis.

SUMARIO

1. Para confirmar el diagnóstico en un enfermo en estado general relativamente bueno en que se sospecha tuberculosis, hay que obtener una reacción positiva a la tuberculina.

2. En toda serie numerosa de enfermos con radiografías indicativas de tuberculosis se encontrará cierta proporción que no reaccionan a la tuberculina a concentraciones altas. En esos casos simplifica el diagnóstico diferencial el conocimiento de que el tuberculoso pulmonar activo que es anérgico encuéntrase siempre en estado crítico. Independientemente de los hallazgos roentgenológicos, no todo paciente anérgico que no parece enfermo, es tuberculoso.

3. Jamás se encuentran bacilos tuberculosos en el esputo de un enfermo anérgico, a menos que éste se halle en estado crítico.

4. El tuberculoso anérgico es mucho más susceptible de mostrar grandes cantidades de bacilos tuberculosos en el esputo, que el enfermo muy alérgico.

5. Las comprobaciones sistemáticas con tuberculina constituyen uno de los más importantes aportes del laboratorio al diagnóstico de la tuberculosis.

Acknowledgments

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TUBERCULIN PATCH TEST[1]

A Screening Procedure to Discover Tuberculin Reactors in Children

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In 1941 (1) one of us compared the relative efficiency of the tuberculin patch test and the Mantoux test. At that time it was reported that in presumably healthy children, whose tuberculin sensitivity was known, there was an agreement of approximately 95 per cent. In that study the Mantoux test was carried out with dilutions of OT and no reaction was considered final unless a test was done with at least 1 mg. of OT if higher dilutions did not produce a reaction. It was further indicated in this report that in no case where the patch test was definitely positive, was the Mantoux test negative. As a direct result of this study it has been the practice in our Clinic to use the patch test as a first test and to do Mantoux tests only when the patch test was negative or questionable but had previously been positive.

Recently the opportunity presented itself of using the patch test as a screening procedure in a previously untested group of Negro children ranging in age from infancy to 18 years. This study was undertaken to determine negative reactors who would be eligible for BCG vaccination. No information was sought as to the previous tuberculin reactivity of the persons concerned in the study. Furthermore, the work was carried out under field conditions of operation; that is, mass testing with reading schedules to be kept at definite times.

The routine consisted in applying the patch (commercially obtained) to the skin in the interscapular region previously cleansed with acetone and sometimes with alcohol. The patches were applied by field nurses. Instructions were given to remove the patch in forty-eight hours and to report back for reading forty-eight hours after removing the patch. The areas of reaction were measured and the number of papules were recorded as few, moderate or many. Roughly, our readings corresponded to the gradient stated by Furcolow and Robinson (2) of +, ++ and +++, respectively. Because it has been our experience that a reading of few papules or vesicles in the area of reaction is not always reliable in the light of subsequent Mantoux tests with 1 mg. of OT, it was decided not only to do Mantoux tests in this study on all negative patch reactors but also on those who gave only a weakly positive or 1+ reaction.

The Mantoux reactions were read at forty-eight hours and only those with a minimal diameter of 5 mm. of induration were considered positive. Reactions of less than this degree were considered questionable and those with no discernible reaction were called negative.

The results were as follows:

Total number of patches applied and read		2,259
Patch test positive	581	

[1] From the Tice Clinic of the Municipal Tuberculosis Sanitarium of Chicago and the Department of Pathology and Bacteriology of the Chicago Medical School, Chicago, Illinois.

Patch test negative	1,382	
Patch questionable*	296	
Total number of Mantoux tests (1 mg. OT)		1,542
Mantoux test positive	287	
Mantoux test negative	1,059	
Mantoux questionable**	196	

* Questionable patch readings consisted of "few vesicles or papules in area of reaction."
** Questionable Mantoux reading consisted of an area of reaction of less than 5 mm. in diameter.

An analysis of these data reveals that on initial patch test 581 of the 2,259 children were positive. Retesting of the negative and questionable reactors to the patch test with 1 mg. of OT revealed an additional 287 reactors. This indicates an efficiency of 66.9 per cent, that is, only two-thirds of the total number of reactors were revealed by the initial patch test. On the other hand, the initial patch test was negative in 895 instances. In 164 children in whom the patch test was questionable, the Mantoux was definitely negative, indicating an efficiency of 84.5 per cent from this point of view. It should be noted that no consideration was given in this study to the possibility that the intracutaneous injection of 1 mg. of OT could give a negative reaction where the patch test was definitely positive. This fact has been abundantly confirmed in other studies (3).

DISCUSSION

The primary objective in doing tuberculin tests is to determine the presence of tuberculous infection. There have been and are in use several techniques of administration. Up to the present time, most informed opinion is agreed that the intracutaneous injection of graded doses of tuberculin has the highest degree of efficiency. However, there are secondary objectives which deserve consideration when selecting the most suitable method of tuberculin administration. If one is interested in finding only those members of the population who have most likely been exposed to infection or have active clinical disease, the report of Furcolow and Robinson (2) gives evidence that those with a high degree of reactivity only need be considered. Under certain circumstances, according to these investigators, single tests using relatively high dilutions of tuberculin or depending on 2+ and 3+ reactions to patch tests, may be considered effective for case-finding purposes.

Parenthetically, apropos this particular objective, we should like to cite a case that came to light in another study, which will be reported in detail later. In a community under observation for four years, during which annual chest roentgenograms and tuberculin tests were done, the findings in one family are of interest. The family consisted of the parents and 6 children ranging in age from infancy to 7 years, all of whom had negative chest films and tuberculin tests at first, second and third examinations. At the fourth examination 4 children had a mildly positive reaction to the patch test, one had a strongly positive reaction and one had a negative reaction. No chest films were taken at that time. At the fifth examination, the tuberculin reactions were strongly positive in all the

children and chest films revealed roentgenological findings compatible with active primary tuberculosis in 2. A third child, the youngest, had developed a tuberculoma of the brain in the region of the pons and subsequently died. The chest films of the mother and father at this time were still completely negative. Investigation of all possible contacts among neighbors and friends finally resulted in the discovery of the source of the infection in a far advanced open case of tuberculosis in the "boy-friend" of an aunt of the children who had visited with the family rather frequently during this period.

In this study we were not interested in case-finding but in determining negativity to tuberculin. The most accurate method necessitates at least two intracutaneous injections of either PPD or OT. Under the conditions of field work, the use of injections often leads to a rebellious attitude and reduces coöperation. To minimize this particular objection and yet retain accuracy of results, we have attempted to test the efficiency of replacing the first intracutaneous test with a patch test.

The results have been reported above and analysis does not speak highly for the relative efficiency of the patch test. However, on the basis of ease of administration and community coöperation, we feel that our objective has been accomplished.

CONCLUSION

In previously untested children the patch test may be used as a screening procedure to determine negativity to tuberculin.

CONCLUSION

En niños previamente no comprobados puede utilizarse la prueba del parche como procedimiento de selección para determinar la negatividad a la tuberculina.

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CELLULAR RESISTANCE TO PULMONARY TUBERCULOSIS AND PULMONARY INTRAVASCULAR PRESSURE

FERDINAND RODER[1]

The thesis that a causal relationship exists between pulmonary intravascular pressure and resistance to pulmonary tuberculosis was set forth by me in a paper read before the society of physicians of Vienna on July 3, 1920 (1). Independently of it, this relationship was recently restated by William Dock (2). His and my explanations of this relation are, however, fundamentally different. It is the purpose of this paper to make this difference clear.

Observations of various facts in certain fields of biology had led me to the conclusions that the dependence of vitality or cellular resistance upon pressure is a universal principle of living matter, and that this causal relation is not based on the natural connection which exists between circulation and supply of potential energy and which is so obvious in higher animals, but on the not so obvious effect which varying pressure itself produces in the cells. I applied this view to the particular phenomenon of apical predilection for pulmonary tuberculosis and to the general phenomenon that in different places as well as in the same region (for instance in the apices) identical cells show different degrees of resistance. Both phenomena seemed explained by my view since capillary pressure must be higher at the bases of the lungs than in the region of the apices and since, due to local functional or anatomical conditions, it cannot be the same in all parts of the same region. The phenomena considered are unexplainable by the concept of some unknown chemical agent, because it is inconceivable that such an agent should be effective at one place and ineffective at another place of the same organ. I, therefore, based my theory of cellular resistance to pulmonary tuberculosis on the following facts.

Pulmonary tuberculosis is frequent in subjects with *cor pendulum* and in pulmonary stenosis; it is rare in mitral stenosis and kyphoscoliosis. In the last mentioned condition the protection is mainly dependent on the condition of the heart; tuberculosis becomes more frequent when myocardial degeneration sets in. Establishment of artificial pneumothorax causes, as direct measurements have shown, increase of pulmonary intravascular pressure. Since also the outflow of blood in the pulmonary veins is rendered more difficult by the introduction of air into the pleural cavity, capillary pressure must rise for both reasons. Examination of the collapsed lung at autopsy shows engorgement of the arteries and veins of the lung and empty capillaries. This fact together with the proved fact that the blood content of the collapsed lung is less than under normal conditions and also less than that of the other lung demonstrates how high the pressure must have been to which the lung tissue was subjected during life, since it is able to drive out the blood in both directions and to congest arteries and veins notwithstanding the diminished blood content. The increased pulmonary pressure puts an extra burden on the right chamber. If long enough continued, this leads to hypertrophy of that part of the heart.

[1] 216 West 100th Street, New York 25, New York.

If hypertrophy fails to develop and dilatation is the only effect of increased pulmonary pressure on the heart, the case history often reveals that collapse therapy, too, has failed to produce its usual beneficial effect. Fibrosis, the somatic expression of higher vitality of the connective tissue and the desired aim of every tuberculosis therapy, is found in the collapsed lungs of normal animals, where there is certainly no chemical stimulus at work. It is also found in the uninvolved parts of the diseased lung and in the lungs of patients with mitral stenosis. All these conditions have in common an increase of pulmonary capillary pressure. The same constant relation is found in our long established and efficient methods of therapy: prolonged bed-rest, pneumothorax and high altitude. What they have in common is again increase of pulmonary capillary pressure. In practical application, this theory would open up new ways of therapy, which could be used either alone or in combination with established methods. I summarized my paper with the statement that the essential factor in the susceptibility of the apices to pulmonary tuberculosis is a low capillary pressure; the essential factor in protection against it and in the healing of it is the natural or artificial increase of pulmonary capillary pressure.

William Dock bases his theory on recent quantitative data (3) on the pressure in the right ventricles in man, which "have made it obvious that the effective arterial pressure in the cephalad third of the lungs is almost nil when an adult is in the erect posture. At such times the apical parts of the lungs have practically no pulmonic arterial inflow, and certainly no formation of tissue fluid or lymph." Because of the gravity effect of the blood column extending from the centre of the right ventricular cavity to the apex of the lung, which antagonizes the systolic pressure, "the pulmonic arterial pressure in the upper 5 cm. of the lung, even in systole, rarely can be more than 10 mm. Hg." "Since it requires nearly 15 mm. Hg pressure to overcome the difference in colloidal osmotic pressure between the plasma and the tissue fluid, no tissue fluid or lymph will be produced by filtration in the cephalad parts of the lungs of most adults while they are in the erect posture. Also, the flow of arterial blood will fall to zero, or at best to a small fraction of that at the lung bases." The author supplements his statements by a footnote: "It is now known that . . . mean effective pressure in the pulmonic arch is 12 to 16 mm. Hg when recumbent." From these premises he draws the incontestable inferences that during most of the waking hours removal of bacteria into the lymph nodes will be suspended, as will the removal of toxic bacterial products, their neutralization and dilution by lymph, and the supply of antibodies and blood-borne phagocytes. Confirmation of this theory is found in the frequency of tuberculosis in pulmonic stenosis, in its rarity in mitral stenosis, in the susceptibility of tall narrow-chested people, in the higher incidence of initial lesions of the right apex as contrasted with those of the left, and in the great frequence of silicotic lesions at the apex. Deficient removal of the dust particles and deficient dilution of them by lack of phagocytes and lack of lymph, respectively, explain the last mentioned phenomenon.

The premises on which Dock builds up his theory of apical localization of phthisis are listed by him as indisputable facts. They seem to me to be untenable for the following reasons.

(*1*) No clear distinction is made between effective pressure causing circulation and effective pressure causing plasma filtration. This confuses the issue. If what is meant is pressure causing circulation, then the pressure is not truly represented by the mean pressure. The real measure of the kinetic energy of the blood is systolic pressure. To it has to be added the "sucking" factor of circulation, which acts in the same direction. Both together add up to at least 27 mm. Hg and both increase during each inspiration. This has been corroborated by recent experiments (4, 5) which show a great increase of blood flow and blood content of the lungs during each inspriation.

(*2*) If by effective mean pressure is meant the pressure which effects plasma filtration, nothing would be gained by recumbency, since the mean effective pressure in the pulmonic arch is 12 to 16 mm. Hg when recumbent and 15 mm. Hg are required to overcome the difference in colloidal osmotic pressure between the plasma and the pulmonary tissue fluid. As capillary pressure is certainly more than one millimeter lower than arterial pressure, the formation of plasma filtrate would be practically zero throughout the lungs when the subject is recumbent.

(*3*) Whatever is meant by effective pressure, the assumption that because of the very low blood pressure no plasma filtrate and lymph can occur in the upper third of the lung while the subject is erect is inconsistent with the fact that the lung has a double blood supply, the pulmonary artery supplying blood for oxygenation, the bronchial artery supplying blood for nutrition, that is, for formation of plasma filtrate. The pathogenesis of the hemorrhagic infarct of the lung shows what happens to any part of the lung if the formation of plasma filtrate is suspended, even for a short time, and, thus, a condition created which is claimed to exist continuously, as long as the subject is erect, in a large part of the lung. That pulmonary necrosis is produced by lack of capillary pressure as well as by lack of plasma filtrate is proved by the fact that occlusion of a pulmonary artery in a normal lung is not followed by infarction, but only in lungs in which the capillaries are overdistended by preëxisting venous congestion. In such lungs, because of the disproportion between the capacity of their circulatory bed and the blood volume, which is further reduced by hemorrhage into the alveoli, the capillary pressure must actually approach zero. The dryness of the infarcted area, as found at autopsy, demonstrates that under this condition formation of plasma filtrate actually does not occur. Nothing of this kind occurs in a normal lung when the blood supply from the pulmonary artery is suddenly cut off; this proves that, even in this extreme case of complete and permanent cessation of blood flow from the pulmonary artery, formation of plasma filtrate and lymph flow continue in the affected area by means of the auxiliary circulation provided by the bronchial arteries.

Although a wrong premise invalidates all conclusions drawn from it, the following points should be emphasized: (*1*) Rich (6) concluded that the marked concentration of dust at the apex is due to scar formation, which is far more common in the apices than elsewhere in the lung and that, by analogy, tubercle bacilli may be expected to settle more frequently in the apices in adults. (*2*) Blood-borne phagocytes disappear after a few hours, being replaced by phago-

cytic cells of local origin. (*3*) According to Dock's statement, one consequence of his theory, namely, minimal removal of oxygen from apical alveoli due to decreased blood flow and, therefore, the creation of an atmosphere, optimal to support the metabolism of the tubercle bacilli, "is probably not an important factor in apical localization" (2). (*4*) Conclusive experimental "evidence for the absence of any appreciable postural effect on the cardiac output" has been given by Grollman (7). His results show that cardiac output is constant with varying postures, that it is the same in the standing, sitting or recumbent position. In other words, the gravity effect on pulmonic arterial inflow is fully compensated in normal individuals by circulatory adjustments of the human organism. Compensation applies, of course, only to the source of blood pressure, it does not apply to local differences of capillary pressure caused by local differences of gravity.

SUMMARY

Apical localization of tuberculosis and individual cell resistance are explained by the causal relationship existing between capillary pressure and "cell vitality" or "cell resistance." This dependence of resistance to pulmonary tuberculosis upon pulmonary intravascular pressure is evidenced by various facts of pathology and clinical medicine. It is a special case of a universal principle recognizable in living nature.

The explanation of apical localization of tuberculosis, as given by William Dock, is, in my opinion, not tenable.

SUMARIO

La relación etiológica que existe entre la presión capilar y la "vitalidad celular" o "resistencia celular" explica la localización apical de la tuberculosis y la resistencia individual. Varios hechos patológicos y clínicos ponen de manifiesto esa dependencia en que se encuentra la resistencia a la tuberculosis pulmonar con respecto a la presión intravascular pulmonar, tratándose de la aplicación especial de un principio universal reconocible en la naturaleza viviente.

En opinión del A., carece de base la explicación de la localización apical de la tuberculosis, ofrecida por W. Dock.

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ATTEMPTED CAVITY CLOSURE WITH TRANSTHORACIC PLASMA INJECTION[1]

H. M. MAIER AND ALBERT GUGGENHEIM

Spontaneous closure of tuberculous cavities has been known to occur for many years, but until recently the true mechanism involved was not clearly understood. Only since the investigations by Pagel (1), Coryllos (2, 3), Eloesser (4), Monaldi (5) and others, has the importance of bronchial factors been recognized in the formation as well as in the closure of cavities.

Long before obstruction and narrowing of bronchi had been assumed to be major causes of cavity closure, various substances were injected into tuberculous cavities to sterilize the cavity walls and stimulate the formation of granulation tissue. None of the substances used produced the expected results, nor did attempts to obliterate cavities by grafting of healthy tissues into the cavities prove successful.

During the past decade numerous investigators have tried to close cavities by artificial obliteration of the draining bronchi. However, permanent bronchial occlusion has not been achieved in man either by cauterization or by the introduction of occluding foreign substances (Pinner (6)). Several years ago attempts were made at the National Jewish Hospital (7) to close draining bronchi during Monaldi aspirations by cauterization of the bronchial mucosa. Neither electrocautery nor the applications of sclerosing agents produced a permanent occlusion of the bronchial lumen.

Artificial occlusion of the bronchi of residual cavities after Monaldi aspiration has been attempted by injecting various substances through the drainage catheter (5, 11). A mixture of magnesium silicate and aluminum silicate in collodion was used; later on, a mixture of charcoal and keratin dissolved in collodion. Complications such as activation of pericavitary foci, secondary infection of the cavity and infection of the transthoracic tract occurred.

In 1943, Thomas (8) published a preliminary report describing a new approach to the problem of cavity obliteration. Plasma obtained from the patient's blood was mixed with calcium chloride and injected through a Monaldi catheter into residual cavities. Bronchial occlusion could be demonstrated roentgenologically by means of contrast media added to the plasma. Filling of cavities, diminution in size and apparent closure were observed.

In April, 1946, in a personal communication, Thomas (9) stated: "As regards the follow-up of our early experiments, we have undoubted examples of blocked cavities resulting from the methods used. We tend to believe that little of the plasma remained but that we occluded by repeated irritation the draining bronchi already partially stenosed by disease."

Although the number of cases treated was relatively small, we felt that the method was safe and promised to produce at least temporary occlusion of bronchial lumina.

[1] From the National Jewish Hospital at Denver, Dr. Allan Hurst, Medical Director, and the University of Colorado School of Medicine, Denver, Colorado.

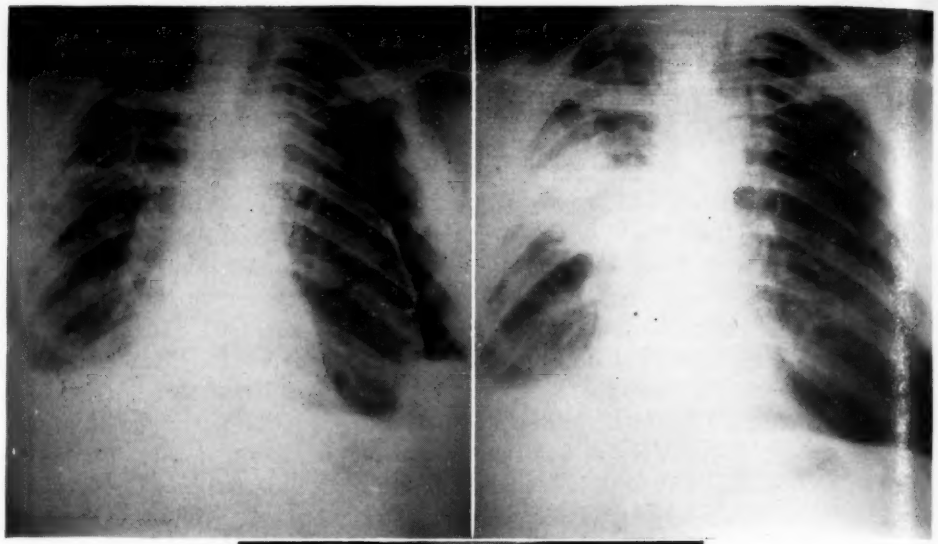
PROCEDURE

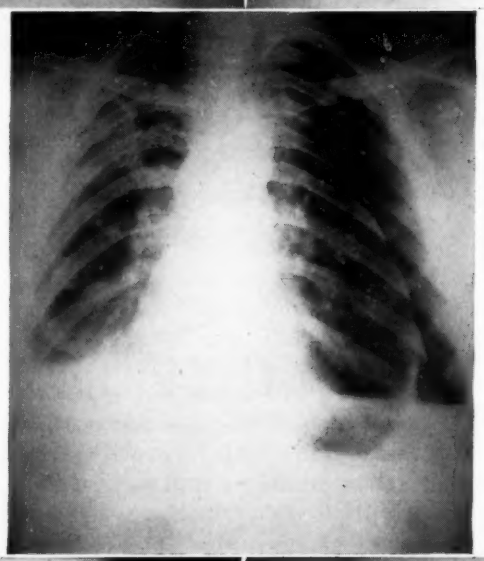
We considered at first the bronchoscopic instillation of plasma, but, because of the technical difficulties involved, we decided to inject the plasma mixture directly into the cavity by the transthoracic route. For coagulation, thromboplastin-calcium chloride was used in the same proportion as in the modified method of Quick for determination of prothrombin time (10). Plasma was obtained from the patient's blood, the prothrombin time determined, and varying amounts of the plasma, according to the size of the cavity, injected through a wide bore needle after intracavitary pressure readings were obtained under fluoroscopic guidance. The injection was timed according to the previously obtained prothrombin time so that the whole plasma mixture was injected into the cavity a few seconds before completion of the coagulation process. Before the procedure and for twenty-four hours afterwards sedative and anti-expectorant medications were given. Patients were selected with isolated cavities for which no surgical collapse procedures could be considered because of various contraindications.

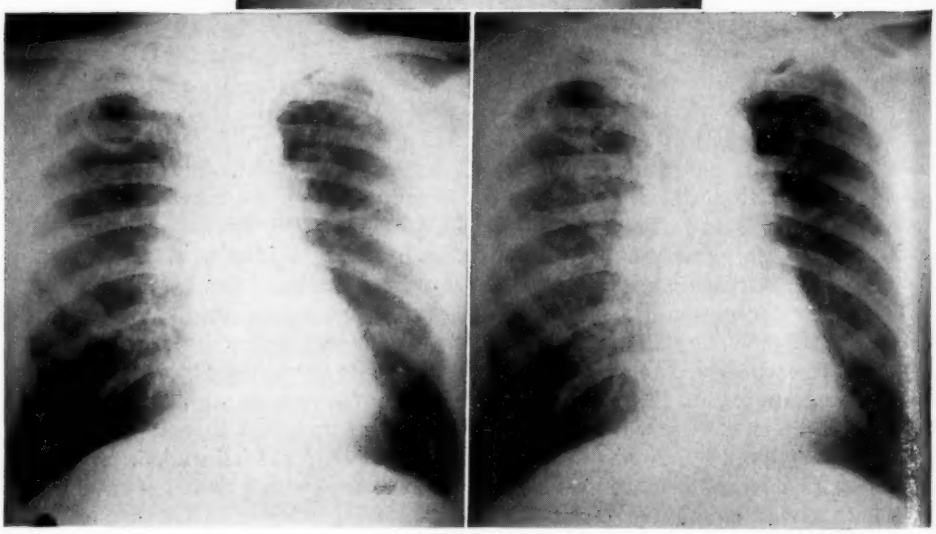
CASE REPORTS

Case 1: F. W., a 33-year-old white male, with a giant cavity in the left lower lobe which had repeatedly closed and reopened in spite of phrenic interruption and pneumoperitoneum. On 1/24/46, the cavity was needled through the sixth posterior interspace in the midscapular line. Initial readings were −12 +2; after withdrawal of air, −54 −38, with return to initial pressures after a few seconds. Sixty cc. of the plasma mixture were injected. On the evening following the injection the patient's temperature was 101°F., and he ran a febrile course, with temperature up to 103.8°F. for the following ten days. An X-ray film on the day following the procedure showed fluid retention in the cavity. Cough and expectoration were markedly diminished during the febrile period, and it was apparent that the plasma injection had resulted in a temporary cavity block with toxemic absorption. Subsequently his temperature returned to normal and serial X-ray films showed no remarkable change in the size of the cavity.

Case 2: B. D., a white male, 34 years of age, with a 4 cm. cavity in the basal axillary portion of the right upper lobe. On 1/11/46, the cavity was needled through the first anterior interspace. Cavity pressures were −8 +2; after withdrawal of air, −16 −4, returning to initial readings after a few seconds, with air being sucked into the cavity through the tracheobronchial route with an audible wheeze. These pressure readings, as in the first case, were suggestive of a weak deflationary check-valve mechanism. Twelve cc. of the plasma mixture were instilled. Following the procedure, cough and expectoration were diminished, X-ray films showed no apparent change. On 1/30/46, the cavity was needled again. Intracavitary pressures were −12 +2; after withdrawal of 30 cc. of air, −24 −8. These negative readings persisted, suggesting a reinforcement of the bronchus-cavity check-valve by the plasma instillation. Fifty cc. of the plasma mixture were again injected. On the day following the procedure, the patient's temperature went up to 101°F. X-ray examination showed an area of homogeneous density at the base of the right upper lobe. Our impression was that this represented an area of atelectasis, possibly with superimposed pneumonitis. On 2/8/46, the temperature went up to 103°F., and the patient was somewhat dyspneic. An X-ray film showed increase of the infiltration. He was given penicillin and sulfonamide over a period of three days with lytic fall of the fever. Serial films showed progressive resolution of the infiltration, going on to complete resolu-







FIGS. 1–5

tion at the end of two weeks. The interpretation from the appearance of the serial films was that part of the plasma mixture by way of the draining bronchus had reached the segmental bronchus supplying the area below the cavity, causing a temporary occlusion with atelectasis and secondary pneumonitis. The cavity itself showed no marked change in size on subsequent fluoroscopy and films (figures 1, 2, 3).

Case 3: I. C., a 51-year-old white male, with a 4 cm. cavity in the right infraclavicular area with a well visualized draining bronchus. On 2/28/46, the cavity was needled through the fourth posterior interspace. Intracavitary pressure readings were −5 +4. Air was freely withdrawn without pressure change. It appeared that the draining bronchus or bronchi were widely patent. Fifty cc. of plasma mixture were injected. An X-ray film following the injection showed a cloudy density in the cavity, representing the coagulated plasma and streaked areas of density below the cavity, probably due to plasma clots in small draining bronchi at the lower circumference of the cavity. Cough and expectoration were diminished. On 3/3/46, the cavity was needled again. The bronchial mechanism appeared unchanged with identical cavity readings. Sixty cc. of the plasma mixture were injected. Following the injection his temperature was slightly elevated for four days and the cavity appeared somewhat smaller. On 3/21/46, the cavity was needled again. Intracavitary pressure readings were −6 ±0. After withdrawal of 30 cc. of air, readings were −24 −8, returning slowly to initial readings. This change in intracavitary pressures was evidently due to alteration of the bronchial mechanism following the second plasma injection (figures 4 and 5).

DISCUSSION AND CONCLUSION

Plasma injection in our 3 cases did not produce permanent bronchial occlusion as observed by Thomas. The slight modification in technique could not be held responsible for the failures to block the cavities. Although the cough reflex had been suppressed, it was thought that the plasma clot was coughed up with sputum after the material had been liquefied within the cavity. By subsequent intracavitary pressure readings, it could be demonstrated that the size of the bronchial lumina was at least temporarily changed but not long enough to cause a dramatic change in size or shape of the cavity. It appears that the plasma did not become adherent to the walls of the draining bronchi.

Although our initial experiments were not successful as far as the closure of cavities is concerned, it seems advisable to continue this or similar methods with different substances. Thomas later used sodium alginate and rabbit serum instead of human plasma, and found the results more satisfactory.

FIG. 1. (Upper left) Case 2. Pneumothorax left. Cavity in right infraclavicular region with recognizable draining bronchus.

FIG. 2. (Upper right) Case 2. Area of atelectasis and pneumonitis below cavity following plasma injection.

FIG. 3. (Centre) Case 2. After resolution of infiltration there is no marked change in size of the cavity.

FIG. 4. (Lower left) Case 3. Cavity in right infraclavicular region with draining bronchi.

FIG. 5. (Lower right) Case 3. After plasma injection cloudy density (probably plasma clot) is seen in lower part of cavity. Streaked areas of density below cavity are probably due to plasma clots in draining bronchi.

SUMMARY

1. Plasma—calcium-chloride-thromboplastin mixtures were injected into tuberculous cavities, using the transthoracic route. Only temporary changes in the size of the cavity as well as in the valve mechanism of the draining bronchi were observed.

2. No irreversible complications occurred. Further studies with injection of biological products appear indicated.

SUMARIO

1. Por vía transtorácica inyectánronse en cavernas pulmonares mezclas de plasma-cloruro-cálcico-tromboplastina, sin que se observaran más que alteraciones temporales en el tamaño de la caverna y en el mecanismo valvular de los bronquios de drenaje.

2. No se observaron complicaciones irreversibles. Parecen hallarse indicados estudios ulteriores con inyecciones de productos biológicos.

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RESEARCH IN TUBERCULOSIS[1,2]

HENRY STUART WILLIS[3]

Always down through the ages there have been those who have asked questions about the phenomena around them. They have planned schemes that would test nature's workings and answer the eternal "why." History records that man's progress has been spotty and irregular (of course from many causes) and that his advancement has been put forward mightily by great individual discoveries or efforts which have nearly always led to many subsidiary forays into the unknown.

In medicine to-day we hear much of research. But what do we mean by the term? Galdston (1) has recently advanced the interesting thought that the activities in this field may be divided into the categories of "search" and "research." He would apply the term search to efforts at the acquisition of fact and would have research mean the relating of fact to function: thus, imagination and the interpretation of fact would fit into the province of research. In this scheme the anatomical studies of Vesalius, for instance, are the product of search; those of Claude Bernard, research. Whether search or research, the world to-day is experiencing a great unfolding of fact and great expression of the "dynamic inter-relationship" of fact.

There must be a certain background to research. Facts of modern physics which made research on the atomic bomb successful have been accumulated gradually since the time of Sir Isaac Newton in the 17th century, but factual data behind the tubercle bacillus are not yet seventy years old. However, this by no means indicates that we must wait for the passage of time to do experimental and clinical study in the field of tuberculosis. It means rather that the field is large and the door is open. It means that the many unknowns in the field stand as a challenge. One prime lack of knowledge may be seen in the fact that those who have worked longest in the field are not even in agreement on the fundamental question of whether immunization against the disease should be attempted. You agree that there ought to be some sort of atomic *Blitz* which would remove tuberculosis from the world for all time; but you will agree also that more knowledge and wider use of existing knowledge are needed.

Do we need more research to-day? Tuberculosis, long the chief killer, is now in seventh place as a cause of death. New methods of diagnosis find cases early. Modern sanatoria abound, modern modes of medical and surgical treatment are in use. Many people live to-day who would have died of this disease if earlier death rates still prevailed. Some ask whether the disease is not under reasonably good control. But the fact is that it remains the chief killer, except for accidents,

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[2] Presented before the Mississippi Valley Conference on Tuberculosis, Chicago, Illinois, September 27, 1946.

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in the most productive and active ages (20 to 35). Tuberculosis is still a challenge which presents many basic problems and unknowns. We ask ourselves why people react in one way to primary infection and in another way to reinfection, but we do not have the answer. Or why the very young are prone to miliary tuberculosis and meningitis. Have we fathomed the nature of the factors which predispose to tuberculosis—that tend to convert mere infection on the one hand to clinical disease on the other? Why are we still unable to provide specific protection against this disease? When and under what conditions will we use BCG? Are we doing all we should in the revival of chemotherapy? These two latter subjects dangle most intriguing possibilities before us in tantalizing fashion, but we are still far from essential guide-lines. In the field of therapy we may wisely call for a new interpretation of rest and a new and more rational application of it. We are far from uniformity in several of the most acceptable measures of surgical treatment. In our own clinical contacts, each one of us daily feels the need of more knowledge, more wisdom.

Do we need research? Ask the man who is presented with a serious diagnostic or therapeutic problem at the bedside. Many men whose work brings them daily into contact with sick people have primary interest in the practical application of medical knowledge and are often impatient with so-called basic or fundamental research. Ideally everyone in medicine should have an absorbing interest in the unexplained phenomena before him. The question "why" should repeat itself so forcibly as to drive him to satisfy his questioning curiosity. We become research workers in proportion to the intensity of our interest, the range of our ingenuity and the depth of our understanding and wisdom. Some carry the "why" and "how" and "what" remotely in mind and find study difficult; others strive constantly to learn the answers. Thus are searches made, researches performed; thus are conditions set up to elucidate fact and to test validity of apparent fact or circumstance. Can we not, then, say properly that research is a state of mind—an attitude of life—a questioning of the hows and whys of the unknowns about us? If so, many can be researchers in spirit and in truth.

A fair amount of research in tuberculosis is currently being carried on, as the AMERICAN REVIEW and other medical journals bear witness. This is mostly done on an individual basis although some of it represents planned group-effort. The Committee on Medical Research of the National Tuberculosis Association supports a good deal of study. A word about its activities may be in order. In 1920, Gerald Webb, then President of the Association, named to a Committee on Medical Research Paul Lewis, Allen K. Krause and Wm. Charles White, the latter chairman. The Committee established its plan. It had but little money. This it wished to invest wisely. By expending small sums for technical assistance and materials the Committee could enable the research worker to utilize his skill and to use the property, equipment and overhead of the university or institution which employed him. The Committee established two general approaches: (*1*) correlated, coöperative research; (*2*) individual research.

The Committee felt that greater progress would be made under a scheme of integration and correlation than by individual effort alone. To this end, broad

subjects on which more knowledge was imperative were selected. Workers skilled in specific fields were asked to participate and thus to conduct their work under Committee sponsorship. This scheme of coördinating research had precedent. It appears that Ehrlich operated a research project in which workers applied their skills in the search for a specific chemotherapeutic agent against syphilis. These workers devised a great number of arsenical preparations which they studied pharmacologically, experimentally on animals and clinically on man before the famous 606 was produced.

The integrated investigation of the Committee stands at its best in the chemical work it has sponsored. In this work Long's synthetic medium was chosen for growing the tubercle bacillus; after growth the medium became the substance upon which Long, Seibert and fellow workers strove for the chemical purification of tuberculin. The tubercle bacilli from the cultures, in the hands of Johnson and later of Anderson, underwent chemical analysis and several chemical entities were isolated which, in turn, were studied biologically in animals by Sabin and her associates in an effort to identify fractions of the bacillus which might be responsible for symptoms of the disease.

The Committee's second approach concerned the support of research efforts of individual investigators. One of the best examples of the type of work supported in this way may be seen in William Snow Miller's anatomical studies of the lung. By providing assisting personnel, equipment and materials, the Committee made it possible for this investigator to extend greatly our knowledge of the lymphatics and blood vessels in the lungs and their relationship to the formation of tubercle, the nature of reticulum and its connection with the progression and healing of tuberculosis, and many other anatomical and pathological relationships in human pulmonary tuberculosis.

It is not the purpose of this paper to delineate items in the history of the Committee, which has been done by Nicolson (2), but rather to indicate by these few examples the general plan on which the Committee has operated since its inception. The range of its work has been relatively broad. It coöperated with the Tuberculosis Control Division of the U. S. Public Health Service and The Henry Phipps Institute in launching the now well-known study of BCG among Indians. More recently it sponsored the study of minimal lesions in conjunction with the Public Health Service.

At present there is under way a group of studies on the chemistry of the tubercle bacillus and the application of various chemical fractions of the bacillus to the animal body. A specific study is in progress on the carbohydrates of the bacillus and two on problems in respiratory physiology; two on the factors responsible for caseation and softening. Another study on histoplasmosis seeks especially to find, if possible, evidence of early infection and its rôle in causing intrathoracic calcification. Also in contemplation is the subject, among others, of sterilization of the air by germicidal lamps.

Of recent years the plea has been voiced by many for more attention to clinical problems—more study of bedside medicine—more research into the phenomena that shroud the sick man and continue to pose unanswered problems for the phy-

sician. In general medicine, research in nonclinical subjects has prospered rather better than those that are strictly clinical, and in tuberculosis this tendency has been marked. Look at the REVIEW. The editor prints all the presentable clinical material that comes to him—yet the dearth of papers on clinical investigations is obvious. Why do we not turn our attention more often to bedside medicine? Why is it that, when clinicians far outnumber those in nonclinical fields, the few among the latter submit the majority of the studies? As an example, the patient's cough offers a real problem which might be studied. There are good reasons for the patient to raise sputum. But when cough is excessive or unproductive, a dozen of us may have a dozen different approaches. But most of us will give codeine. If the cough is not controlled, we increase the dose, not knowing whether this narcotic paralyzes the action of the cilia and thus hinders the raising of sputum. We realize eventually that the cough which a quarter grain will not control is also refractory to a half or a whole grain. Why should we feel that a subject like this is simply unfathomable? Why cannot someone study cough, relate it to the type and location of disease, to posture and ease of expectoration, to ciliary action, and do the thing on a basis of scientific definition that will give us some useful answers? Or take anemia in tuberculosis which also is a relatively unexplored field, or the utilization of food by patients with different types of tuberculosis and complications. There is need for controlled scientific study of bedside problems.

The Committee on Medical Research has a schedule to keep. It is continuing its sponsorship of several of its basic studies. At the same time it recognizes the value and the desirability of attention to individual research in clinical, pathological and bacteriological domains and is prepared to underwrite such increasingly. It is well known that the Committee receives and grants requests from individuals for support of particular studies. Whoever has a study in mind will receive full consideration if he submits his problem to the Committee. To be sure the basis of the study must appear to be sound. The application must bear evidence of a well-thought-out scheme and must include a proposed budget. But the invitation is a standing one. The Committee is ready to help. Will you avail yourself of the opportunity—you who criticize the present scheme and you who do not?

Let us do more study. Let us say with the writer of Proverbs "where there is no vision the people perish." Expansion of roentgenology, of thoracic surgery, of the rationale of bed-rest, of bacteriology, physiology and pathology—all these may lead to magnificent elaboration of fact and attitude. It stands as a challenge to all of us.

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APICAL SCARS[1,2]

Their Etiological Relationship to Tuberculous Infection

E. M. MEDLAR[3]

Scars at the apex of the lung are generally regarded as healed tuberculous foci and, since they usually are bilateral, the theory has been advanced that they are lesions resulting from a postprimary hematogenous dissemination of tubercle bacilli. Rich (1) comments on this problem as follows: "Lesions of the apex are frequently found roentgenologically, but clinically, the great majority of these become permanently arrested and pathologically, they are found as the familiar, obsolete apical scars." Pinner (2) states: "Fibroid phthisis in the strict sense is healed phthisis. Dependent on the extent of the involvement, it may be represented by small, frequently apical scars of no clinical relevance . . . ." Moore (3) reports an incidence of 33 per cent of apical scars in 100 white adults, considering these lesions as healed tuberculosis, and presents on page 303 a photograph of the type of lesion which will be discussed in this paper. MacCallum (4) defines these scars as follows: "Such apical lesions which are generally flat, scale-like, depressed scars over the apex of the lung, often with pigment collected about them, are extremely common in persons of middle and advanced age. They may extend into the lung substance a short way or even lie below the apex, radiating narrow lines of scar tissue into the surrounding lung and sometimes showing a caseous or calcified center. These apical scars on microscopic study rather rarely show any distinct tubercles, but there are so many transitions to a more active process that their nature cannot be doubted." To this description, the author desires to add that they vary considerably in size and shape, are predominantly bilateral with a symmetrical placement on the two sides and rarely exhibit pleural adhesions over the involved area.

During the past two years the author has been collecting, in the Medical Examiner's Department of the Borough of Manhattan, data relative to the incidence of tuberculous infection in cases of unexpected death and, as part of the study, the location and type of apical scars have been carefully recorded. Any reference to tuberculous lesions in the present discussion is on the basis of macroscopic examination which is subject to revision when a complete study, including microscopical examinations, is reported at a later date. The author is of the opinion that the completed study will not greatly alter the impressions gained from the macroscopic examination. In this investigation, cases of extensive lobular or lobar pneumonia, bronchiectasis, pulmonary tuberculosis or neoplasia, local or metastatic, were not included. These rejected cases were practically all in older persons and constituted less than 5 per cent of the material

[1] Sponsored by the Hegeman Memorial Research Fund.

[2] The material for this study was obtained through the courtesy of the Medical Examiner's Department of the Borough of Manhattan.

[3] Associate Professor of Pathology, College of Physicians and Surgeons, Columbia University, New York, New York.

available. Cases with unilateral or bilateral dense obliterative pleural adhesions were not investigated for apical scars. Cases with thin focal or extensive pleural adhesions were carefully studied and not infrequently typical apical scars were observed beneath the pleural adhesions. Otherwise, the only restriction was that every case be thoroughly studied, an average of two hours being required for each necropsy. The author was not responsible for the performance of the general necropsy nor for the recording of the necropsy findings in any of the cases. Persons of Caucasian and of Negro races were investigated and all cases over three months of age were included.

TABLE 1

Comparison of apical scars with age, race and presence or absence of tuberculous foci: 960 white—299 Negro

RACE	TUBERCULOSIS	APICAL SCARS	TOTAL	AGE		
				3 months to 29 years	30 to 49 years	Over 50 years
White	Present	Total	722	54	253	415
		Present	347 (48.1%)	2 (3.7%)	83 (32.8%)	262 (63.1%)
		Absent	375 (51.9%)	52 (96.3%)	170 (67.2%)	153 (36.9%)
	Absent	Total	238	82	89	67
		Present	76 (31.9%)	3 (3.8%)	28 (31.4%)	45 (67.2%)
		Absent	162 (68.1%)	79 (96.2%)	61 (68.6%)	22 (32.8%)
Negro	Present	Total	184	52	94	38
		Present	27 (14.7%)	—	14 (11.7%)	13 (34.1%)
		Absent	157 (85.3%)	52 (100%)	80 (88.3%)	25 (65.9%)
	Absent	Total	115	57	42	16
		Present	9 (8%)	1 (1.7%)	5 (11.9%)	3 (18.8%)
		Absent	106 (92%)	56 (98.3%)	37 (88.1%)	13 (81.2%)

RESULTS

Table 1 presents a comparison of apical scars with reference to age, race and the incidence of macroscopic evidence of tuberculous infection. Fourteen hundred cases were studied but 141 are not included in the data as dense unilateral or bilateral obliterative pleural adhesions, dense pleural adhesions associated with apical tuberculosis or tuberculosis of considerable extent with accompanying pleural adhesions were present. Of the remaining 1,259 cases, 960 were Caucasians and 299 were Negroes.

The relationship between age and apical scars is evident. No apical scars were found in 106 persons under 20 years of age although this group showed an incidence of 21.7 per cent of tuberculous foci. There were 140 cases between 20 and 29 years of age with an incidence of 3.5 per cent with apical scars and 59.3 per cent with tuberculous lesions. In 290 persons over 60 years of age, apical scars were present in 65.9 per cent and tuberculous foci in 88 per cent of the cases. Apical scars occurred as frequently in persons without any evidence of tuberculous lesions in their tissues as they did in those with single or multiple tuberculous foci.

It was found that apical scars occurred more frequently in Caucasians than they did in Negroes, regardless of age. A somewhat similar condition was found relative to sex in Caucasians where apical scars were present in 24.2 per cent of 219 females and in 53.1 per cent of 697 males over 20 years of age. In similar groups of Negroes, apical scars were present in 13 per cent of 85 females and in 17.7 per cent of 141 males. The incidence of tuberculous lesions in these four groups were as follows: white female, 69.2 per cent; white male, 82.4 per cent; Negro female, 61.2 per cent; Negro male, 66.7 per cent. While the white male showed the highest percentage of tuberculous infection, this fact, by itself, does not account for the difference noted in the relation of apical scars to sex and race.

Apical scars were recorded in 459 cases with a bilateral and symmetrical distribution in 446 (97.2 per cent). Nine of the 13 cases with unilateral apical scars were white males, 3 were white females and one was a Negro male who had a large syphilitic aneurysm of the arch of the aorta that protruded into the right chest with the apical scar being at the apex of the right upper lobe, perhaps a contrecoup effect. Focal adhesions were present over the apex of the opposite lung in 7 cases. The bilateral and symmetrical pattern of the apical scars bore no semblance to the asymmetrical and scattered distribution of the tuberculous lesions.

Tuberculous foci contiguous to or directly involving apical scars, which were bilateral, were observed in 33 cases with the tuberculous lesions being unilateral in 26 and bilateral in 7 instances. There were 20 persons who had apical tuberculous lesions with neither apical scars nor focal pleural adhesions. Forty-five persons, not included in the data in table 1, had tuberculous lesions with dense obliterative focal pleural adhesions in the area where apical scars usually occur with the foci being bilateral in 23 and unilateral in 22 instances, the latter group showing no apical scars on the opposite side. It is evident that tuberculous lesions can occur in the apex, unilaterally or bilaterally, with or without apical scars being present.

On occasion a lower lobe of a lung may be unusually large with its apex forming one-half or more of the dome of the lung. Twelve such specimens were observed in this study. In 6 instances, the left lower lobe occupied such a position with apical scars being present in the left lower, the left upper and the right upper lobes. One case showed the left lower lobe occupying two-thirds of the dome of the lung with apical scars present in the left lower and right upper and no scar in the left upper lobe. Another case showed the lower lobe on either side occupying

one-half of the dome of the lung with an apical scar in both lower and both upper lobes. No tuberculous foci were found in 3 of the 8 cases. In the 4 remaining specimens no apical scars were present with 3 exhibiting tuberculous foci. Another case had a large right azygos lobe with apical scars in it and in both upper lobes. Apical scars have not been observed in lower lobes except as noted above, although tuberculous foci have often been found in the upper portions of lower lobes.

DISCUSSION

The observations presented in this paper are concerned primarily with the etiological relationship between apical scars, sometimes called "apical caps," and tuberculous infection. The pathogenesis of these peculiar lesions can be determined only by a study of the process in different age groups when it may be possible to obtain specimens in different stages of development. In the present study, evidence of tuberculous infection is based on the finding of calcified or caseous foci or of tuberculous cavity in the lung parenchyma, in areas dissociated from the typical apical scar, or similar tuberculous foci in lymph nodes or other tissues. Phleboliths, small chondromata and "osteomata" have been observed in some of the cases and such lesions are fairly easily recognized from their macroscopic appearance. Flat calcified or bony plaques were frequently observed in the more superficial portion of apical scars, especially in persons over 50 years of age, and these have not been considered as indicative of tuberculous infection. Had all apical scars been interpreted as tuberculous in nature, the only effect would have been to increase, by a few percentage points, the incidence of tuberculous infection in white persons over 20 years of age. An uncritical acceptance of a tuberculous etiology for all apical scars allows a plausible explanation for the increase of these lesions with age, but the differences noted in relation to sex and race can hardly be accounted for in this manner.

The occurrence of apical scars in lower lobes only when they form half or more of the dome of the lung raises a question which cannot logically be explained on a basis of tuberculous infection. Similarly, the presence of bilateral apical scars without any definite tuberculous lesions in the rest of the tissues is not satisfactorily accounted for by the theory that such lesions are the result of a post-primary hematogenous dissemination of tubercle bacilli. Tuberculous foci do develop in the apex of the lung and they may be bilaterally disposed. They may also be found in the lung tissue contiguous to apical scars which they may involve in the course of their development. On the other hand, the bilateral symmetry of apical scars bears little semblance to the asymmetrical and scattered pattern of tuberculous lesions.

The belief that apical scars are healed tuberculous foci has long confused thought relative to the pathogenesis of phthisis. This confusion has resulted from a failure to distinguish between a strictly tuberculous involvement of the apex of the lung, tuberculous foci contiguous to apical scars and apical scars without any evidence of tuberculosis either in the scarred area or in other tissues of the body. Phthisis may have its inception in an apex and pursue an apico-

caudal course; it may begin infraclavicularly (*Frühinfiltrat*); or it may originate in the upper portions of any pulmonary lobe; and without any relation to apical scars in either instance.

Many of the apical scars noted in this study were of sufficient size and density to cast shadows on a roentgenographic film. Since significant tuberculosis may occur in the same location, it is necessary to try to differentiate between the two conditions. Fortunately, apical scars rarely occur and are always of slight extent below the age of 30 so that in the younger age groups they need not be considered, even if there are bilateral apical shadows. The increasing frequency of bilateral apical scars with advancing age indicates the necessity for caution in the interpretation of apical shadows as tuberculous, especially in white males over 50 years of age. The problem will be less complicated in Negroes for bilateral apical scars, nontuberculous in nature, are infrequent at any age in this race. Shadows of calcium density in the apical region are no sure indication of tuberculous lesions. Since tuberculous lesions in association with apical scars are more frequently unilateral than bilateral, a considerable inequality of the shadows on the two sides would suggest the presence of a tuberculous lesion.

CONCLUSIONS

1. Apical scars were observed in 423 (44.1 per cent) of 960 white persons and in 36 (12 per cent) of 299 Negroes. The incidence of tuberculous infection was 75.2 per cent and 61.2 per cent, respectively.

2. Apical scars were not observed in 106 individuals under 20 years of age. In 403 white males over 50 years of age, they were present in 275 (68.2 per cent) with the lesions being bilateral in 98 per cent. The incidence of tuberculous infection in these two groups was 21.7 per cent and 86.8 per cent, respectively.

3. In white persons over 20 years of age, apical scars were present in 24.2 per cent of 219 females and in 53.1 per cent of 697 males. Tuberculous foci were present in 69.2 per cent of the females and in 82.4 per cent of the males.

4. Apical scars were observed in lower lobes only when the apex of this lobe formed one-half or more of the dome of the lung.

5. Apical scars were present with equal frequency in persons who exhibited no macroscopic evidence of tuberculosis in their tissues and in those who had single or multiple tuberculous foci.

6. No definitive evidence was found to support the theory that bilateral apical scars represent healed tuberculous lesions following a postprimary hematogenous dissemination of bacilli.

7. It appears obvious that typical, bilateral apical scars, sometimes called "apical caps," are not etiologically related to tuberculous infection.

CONCLUSIONES

Las Cicatrices Apicales: Su Relación Etiológica con la Infección Tuberculosa

1. En 423 (44.1 por ciento) de 960 sujetos blancos y 36 (12 por ciento) de 299 negros observáronse cicatrices apicales, en tanto que la incidencia de infección tuberculosa fué de 75.2 y 61.2 por ciento, respectivamente.

2. No se observaron cicatrices apicales en 106 individuos de menos de 20 años. Entre 403 varones blancos de más de 50 años, se hallaban presentes en 275 (68.2 por ciento), siendo bilaterales en 98 por ciento. La incidencia de infección tuberculosa en esos dos grupos representó 21.7 y 86.8 por ciento, respectivamente.

3. Entre las personas blancas de más de 20 años, había cicatrices apicales en 24.2 por ciento de 219 mujeres y 53.1 por ciento de 697 hombres, en tanto que la proporción de focos tuberculosos era de 69.2 y 82.4 por ciento, respectivamente.

4. Sólo se observaron cicatrices apicales en los lóbulos inferiores cuando el vértice del lóbulo dado formaba la mitad o más de la cúpula del pulmón.

5. La frecuencia de las cicatrices apicales fué igual en las personas que no mostraban signos macroscópicos de tuberculosis en sus tejidos y en las que tenían focos tuberculosos aislados o múltiples.

6. No se encontraron datos definitivos que apoyen la teoría de que las cicatrices apicales bilaterales representen lesiones tuberculosas curadas a continuación de una diseminación hematógena postprimaria de bacilos.

7. Parece manifiesto que las típicas cicatrices apicales bilaterales no se hallan etiológicamente relacionadas con la infección tuberculosa.

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PRIMARY AND REINFECTION TUBERCULOSIS AS THE CAUSE OF DEATH IN ADULTS[1,2]

An Analysis of 100 Consecutive Necropsies

E. M. MEDLAR[3]

In 1917, Opie (1) proposed an explanation for a differentiation between tuberculosis in the child and in the adult on the basis that adult tuberculosis is due to a reinfection. "First infection in almost all of those who reach adult life occurs in childhood and has the characters of a first infection in animals since it tends to implicate regional lymphatic nodes." "Apical tuberculosis usually exhibits the characters of a second infection, since it pursues a chronic course and is unaccompanied by tuberculosis of regional lymphatic nodes." Three facts are known, as of to-day, which would seem to warrant a review of the conclusions drawn by Opie. First, tuberculin surveys show that a considerable decrease in the incidence of tuberculous infection in young people has occurred in the past twenty-five years. Second, in recent years a considerable number of tuberculin-negative young adults have developed progressive tuberculosis which, from roentgenograms, cannot be distinguished from the "reinfection" type. Third, while tuberculosis in children has decreased appreciably, adult tuberculosis has not decreased in equal proportion.

The pathological changes observed in children and adults dying from tuberculosis at the present time show the same differences as were present twenty-five years ago. Large caseous lymph nodes continue to be a prominent feature in young children and an infrequent occurrence in adults. Calcified foci are frequently observed in adults and are rarely mentioned in children dying from this disease. On the basis that caseous lymph nodes are indicative of a progressive primary infection and calcified lymph nodes of a healed primary infection, it was thought that it might be possible to determine what proportion of adults were dying from a primary infection and what proportion from a reinfection. It appeared that no reliance could be placed on the presence or absence of calcified foci in the lung in distinguishing between primary and reinfection disease for two reasons: first, it is now known that small caseous foci in areas of endobronchial dissemination can calcify; second, since practically all cases exhibit cavitation to a greater or lesser extent, it would be impossible to determine with certainty whether a calcified primary focus had been present in the lungs.

MATERIAL AND METHOD OF PROCEDURE

One hundred consecutive necropsies on adults over 16 years of age who died from tuberculosis were thoroughly investigated with especial emphasis placed

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[2] The author desires to express his appreciation of the coöperation of the Pathology Department, especially to Dr. D. M. Spain, at Bellevue Hospital, New York City.

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upon a painstaking study of the thoracic and abdominal lymph nodes. The material used came in very large part from the Chest Division of Bellevue Hospital.

The contents of the thorax were removed *en masse* and all lymph nodes found adjacent to bronchi, in the pleura and in the mediastinal contents were individually searched for macroscopic evidence of caseation, calcification and fibrosis. A similar procedure was used for the abdominal lymph nodes. The abnormal conditions and the location of the nodes in which lesions were observed were carefully recorded for each case. Fresh, unfixed specimens were examined on removal or soon thereafter. This procedure was chosen because formalin fixation hardens lymphoid tissue so much that fibrosis cannot easily be detected and discovery of minute foci of caseation and of calcification is rendered difficult. The lymph node texture was determined by palpation with bare fingers. Each node was sliced into sections about one millimeter in thickness with a sharp scalpel which proved of great value in the detection of minute foci of calcification and in appreciating the density of the tissue. It took from two to three hours to complete the examination of the lymph nodes in each case.

All lungs were carefully examined for the presence of cavity formation and, if more than one cavity was found, an estimate as to which cavity might be the oldest was made on the basis of fibrotic tissue and the appearance of the cavity wall. In those cases in which little pathological changes other than miliary tubercles were present, a careful search for the presence of small calcified foci which might represent the remnants of a healed primary infection was made. In such cases, the lung parenchyma was cut into slices of tissue about 5 millimeters in thickness and each slice was palpated with bare fingers. The mucosa of the entire gastro-intestinal tract was carefully inspected for the presence of tuberculous ulceration.

For a comparison of tuberculous infection in children with that in adults, 100 consecutive routine necropsy protocols of children below 10 years of age who died from tuberculosis in Bellevue Hospital were used. From each record was abstracted information as to involvement of lymph nodes in the thorax and in the abdomen, cavity formation in the lung and tuberculous ulceration of the intestine. In so far as the involved lymph nodes are concerned, these records did not contain as detailed information as was recorded in the adult cases used in this investigation, but in each protocol there was mention of the presence or absence of caseation in both thoracic and mesenteric nodes. It is possible that small caseous foci might have been observed in the nodes of those cases in which no lesions were mentioned had a very thorough search been made.

RESULTS

A comparison of the lesions found in the thoracic lymph nodes in the children and in the adults with reference to race is presented in table 1. There was a considerable variation in the number and size of the caseous nodes in the children, with the Negro children, as a whole, showing more extensive lymph node changes. Of the 6 children on whom there was no record of caseation or calcification in the

nodes, 5 were white children. In one of the 6 cases, no caseous focus was found in the lungs. This child had a tuberculous ulcer of the intestine with caseous mesenteric nodes and died from generalized miliary tuberculosis, apparently a primary intestinal infection. In the 5 remaining cases, small caseous parenchymal foci were described in 3 and subapical tuberculous cavities in 2 instances. Death was due to generalized tuberculosis with meningitis in 3, and extensive caseous pneumonia in 2 cases. The 3 cases with calcified nodes were white children all of whom had extrapulmonary tuberculous foci and died from generalized miliary disease, 2 having meningitis. In one case, a small puckered scar was observed in the lung, and in 2 cases, small caseous and calcified parenchymal foci were noted.

TABLE 1

Condition of thoracic lymph nodes in individuals dying from tuberculosis Children and adults compared according to race

RACE	TOTAL	CONDITION OF THORACIC LYMPH NODES			
		Caseous	Calcified	Calcified and caseous	No caseation or calcification
Children under 10 years					
Total.....	100 (100%)	91 (91%)	*3 (3%)	—	†6 (6%)
White.....	63 (100%)	55 (87.3%)	3 (4.8%)	—	5 (7.9%)
Colored.....	37 (100%)	36 (97.3%)	—	—	1 (2.7%)
Adults over 16 years					
Total.....	100 (100%)	34 (34%)	26 (26%)	17 (17%)	‡23 (23%)
White.....	73 (100%)	18 (24.5%)	22 (30.1%)	13 (17.9%)	20 (27.5%)
Colored.....	27 (100%)	16 (59.3%)	4 (14.8%)	4 (14.8%)	3 (11.1%)

* 10 year white male, 4 year white male, 4 year white female.

† 10 year colored male, 8 year white male, pos. micro., 2½ year white male, 2 year white male, 1½ year white female, 1½ year white male.

‡ 13 examined microscopically, 12 had microscopic tuberculous foci.

In a number of the adult cases in which the lymph nodes are recorded as caseous, only a small focus, at times not over two millimeters in diameter, was found in a single node. Such lymph nodes were of normal size and appearance and the involvement would have been missed had not the nodes been cut into thin slices. In some cases, several lymph nodes were enlarged and entirely caseous. This condition was more frequently seen in the colored race.

The calcification noted varied from a single focus not over one or two millimeters in diameter in a single lymph node to one or two completely calcified nodes. In the cases where both calcified and caseous foci were observed, they were in all but 2 cases in lymph nodes which drained different areas of the pulmonary tissue. The areas of calcification were usually of small size and were

confined to one or two lymph nodes. The caseous foci were usually of small size but in a few instances the extent was as great as that found in cases in which caseous lymph nodes only were observed. Had not a thorough sectioning of all lymph nodes been done in every necropsy, the coexistence of calcified and caseous nodes would have been missed in nearly all of the cases. This is well illustrated by the case of a white male, 76 years of age, who died from generalized miliary tuberculosis with tuberculous meningitis. Two soft caseous nodes were easily demonstrated adjacent to a branch of the pulmonary artery to the right lower lobe with one of the nodes having eroded through the wall of the artery, thus becoming the source for the general dissemination. The pulmonary parenchyma directly supplied by this artery was so heavily seeded with tuberculous foci that no old parenchymal focus was found. On the left side, a two millimeter calcified focus in a single lymph node adjacent to the left lower lobe bronchus and a one millimeter calcified lesion in the parenchyma of the lower lobe 3 mm. beneath the diaphragmatic pleura were observed.

Failure to find either caseous or calcified foci in thoracic lymph nodes was wholly unexpected. In 2 of the 23 cases, calcified mesenteric nodes were present. In 21 cases, no macroscopic evidence of either caseation or calcification in lymph nodes was found anywhere. Macroscopic evidence of fibrosis was obtained in some of the cases but when this was present the distribution was bilateral and at times quite extensive. Because of the pattern and of the coexistence of a considerable degree of pneumonoconiosis in such cases, the fibrosis was not regarded as evidence of a healed tuberculosis. Two-thirds of the cases revealed no macroscopic abnormality aside from the accumulation of black pigment. Histological sections were made of lymph nodes from 13 of the cases, some with and some without macroscopic evidence of fibrosis, and in 12 of them microscopic tuberculous foci were found irrespective of the presence or absence of fibrosis. This demonstrates that tubercle bacilli had gained entrance to the lymphatics and that a macroscopic examination of lymph nodes is inconclusive as to the presence or absence of minute tuberculous foci.

The differences in the lymph node changes between the child and the adult is evident. The extent of caseation of lymph nodes was, when present, considerably less in the adult, with individual exception. On the other hand, calcified foci and absence of macroscopic lesions were much more frequent in the adult. There is a somewhat similar difference between the white and the Negro adult.

The condition of the thoracic lymph nodes in relation to different age groups is presented in table 2. In the routine necropsies of children under one year of age, caseous lymph nodes were recorded in every case. The similarity in distribution of the different conditions in the lymph nodes in children above one year of age and in adults between 16 and 29 years of age is quite striking, especially with reference to the frequency of caseous foci and the infrequency of uninvolved lymph nodes. Contrariwise is the high incidence of calcified and of uninvolved lymph nodes and the very low incidence of caseous foci in cases over 50 years of age. This contrast in age groups suggests that perhaps the age of the individual more than a blockage of the lymphatics may have a bearing upon the type and the extent of tuberculous involvement of lymph nodes.

The possibility of a primary tuberculous infection originating in the intestinal tract is well known. It is necessary, therefore, to investigate the mesenteric lymph nodes in all tuberculous cases when the question of primary and reinfection disease is under consideration. And in such a study, the relationship of tuberculous cavity in the lung to tuberculous ulceration of the intestine and to caseous mesenteric lymph nodes must be determined. Such a comparison is presented in table 3.

In the children there was but a single case where it seemed probable that the primary infection occurred in the intestine, while in the adult 7 cases showed old calcified mesenteric nodes suggesting that at least this number may have had a primary intestinal infection. Caseous mesenteric nodes were recorded two and one-half times as often in the routine necropsy records of the children as the

TABLE 2

Condition of thoracic lymph nodes in individuals dying from tuberculosis
Children and adults compared according to age

AGE	TOTAL	CONDITION OF THORACIC LYMPH NODES			
		Caseous	Calcified	Calcified and Caseous	No caseation or calcification
Children under 10 years					
Total.....	100 (100%)	91 (91%)	3 (3%)	—	6 (6%)
Under 1 year .	26 (100%)	26 (100%)	—	—	—
1 to 5 years...	54 (100%)	48 (88.8%)	2 (3.7%)	—	4 (7.5%)
5 to 10 years..	20 (100%)	17 (85%)	1 (5%)	—	2 (10%)
Adults over 16 years					
Total.....	100 (100%)	34 (34%)	26 (26%)	17 (17%)	23 (23%)
16-29.....	16 (100%)	12 (75%)	1 (6.3%)	1 (6.3%)	2 (12.4%)
30-49.....	49 (100%)	20 (40.8%)	8 (16.3%)	10 (20.4%)	11 (22.5%)
50 or older....	35 (100%)	2 (5.7%)	17 (48.6%)	6 (17.1%)	10 (28.6%)

author found them in the adult, while no calcified mesenteric nodes were mentioned in the records of the children.

The 38 cases with pulmonary cavities in the children were so recorded in the protocols. In addition, there were 4 cases in which bronchi, eroded by caseous lymph nodes, were considered as the source for caseous pneumonia. Several cases had a description of bronchogenic dissemination, and in these cases ulcerative tuberculous lesions discharging bacilli into the bronchi must have been present. Small cavities are often missed in pulmonary tuberculosis in children because of insufficient search. From these considerations, one may judge that tubercle bacilli had been swallowed by most, if not all, of the children in whom caseous mesenteric nodes were recorded and in whom tuberculous ulcers of the intestine were also found. Under the circumstances, it is significant to find such a close correlation between pulmonary cavitation, intestinal ulceration and caseous mesenteric nodes.

Only 21 of the 89 adult cases with tuberculous cavity in the lungs exhibited caseous mesenteric nodes, and no such nodes were found in 11 cases without pulmonary cavitation. Tuberculous ulcers of the intestine were present in one-half of the cases with pulmonary cavity and in none of the cases without it. Of the 21 cases which had caseous mesenteric nodes, 19 had tuberculous ulcers of the intestine. In 2 cases the author failed to find evidence of intestinal ulceration where caseous mesenteric lymph nodes were present.

TABLE 3

Relation of caseous mesenteric lymph nodes to cavity in the lung and ulceration of the intestine

Children and adults compared

MESENTERIC LYMPH NODES	TOTAL	LUNGS		INTESTINES	
		Cavity	No cavity	Ulcer	No ulcer
Children under 10 years					
Total.....	100	38 (100%)	62 (100%)	*40 (100%)	†60 (100%)
Caseous.....	43	25 (65.5%)	18 (29%)	35 (87.5%)	8 (13.3%)
No gross caseation.....	‡57	13 (34.5%)	44 (71%)	5 (12.5%)	52 (86.7%)
Adults over 16 years					
Total.....	100	89 (100%)	11 (100%)	45 (100%)	55 (100%)
Caseous.....	17	17 (19.5%)	—	15 (33.3%)	2 (3.6%)
Calcified.....	3	3 (3.4%)	—	1 (2.2%)	2 (3.6%)
Calcified and caseous	4	4 (4.5%)	—	4 (8.8%)	—
No gross calcification or caseation ...	76	65 (73%)	11 (100%)	25 (56%)	51 (92.8%)

* In 15 cases with intestinal ulcer, no pulmonary cavity was mentioned. In 6 of these cases, bronchogenic spreads, and in 4, ulceration of a bronchus were mentioned.

† 13 showed pulmonary cavity.

‡ 6 of these showed microscopic tubercles; 3 pulmonary cavity—3 no cavity; 4 with intestinal ulcer; 2 no ulcer.

Caseous thoracic lymph nodes were present in 18 of the 21 adult cases with caseous mesenteric lymph nodes; 10 had caseous nodes only in both situations; 5 had calcified and caseous thoracic and caseous mesenteric nodes; 2 had caseous thoracic with calcified and caseous mesenteric nodes; and in one case, calcified and caseous nodes were present in both sites. In the 3 remaining cases there were calcified thoracic nodes with caseous mesenteric nodes present in 2 and calcified and caseous nodes in one.

DISCUSSION

There are two facts with which all investigators will agree: first, a first infection with the tubercle bacillus in the child usually results in an extension from a

parenchymal focus through the lymphatics to regional lymph nodes which generally become entirely caseous; second, if and when the primary focus heals, calcified foci commonly remain as mute evidence of the healed infection. This relationship between parenchymal foci and lymph nodes in the drainage path, first reported by Parrot (2) in 1876 and later corroborated by Küss (3), Ghon (4), Opie (1), Schürmann (5), Sweany (6) and Terplan (7), to name a few, has had great influence upon the interpretation of tuberculous infection in the adult. Some investigators would not entirely agree with Schürmann (5) who maintains that this combination, commonly called the Ghon complex, is an absolute pathognomonic entity.

Disagreements appear in reports on primary infection in the adult. Ghon (4), Terplan (7) and Ragnatti (8) claim that the Ghon complex is the same in adults and children, although Ragnatti believes that a primary infection is rare after the age of 15 years. Sweany (9) found that primary infections in the adult behave differently from those in children. Opie (1) found that "almost all human beings are spontaneously 'vaccinated' with tuberculosis before they reach adult life." Blumenberg (10) observed that primary infections in adults are not characterized by involvement of lymph nodes, and he believes that this difference is influenced more by the age of the individual than by the allergic state.

A majority of investigators agree that phthisis is a reinfection phenomenon. Some think that this condition is the "relighting" of a smouldering unhealed focus derived from a primary infection which they call an "endogenous reinfection"—a wrong usage of the term reinfection.[4] Others use the term reinfection in its correct meaning, that is, a new exogenous infection after a first infection has completely healed. Pinner (11), for instance, in discussing immunological principles relative to data obtained from animal experimentation states: "Only a well considered interpretation of the infection-reinfection experiments established the recognition that human phthisis is a reinfection tuberculosis, that infection and disease, identical in experimental animals, are two nosologically distinct entities in man, which in the animal can at best be approximated but can be reproduced only under exceptional circumstances." There seems to be general agreement that there is no lymph node involvement in a reinfection disease and an "allergic state" is claimed to be responsible for this phenomenon. Recently Terplan (12) has reported cases in which a reinfection found in persons dying from other causes behaved just like a primary infection; and the author has evidence, not yet published, which corroborates these observations. On this question, Rich (13) comments as follows: "For the present purpose, it is sufficient to recognize that, while occasional individuals may lose the resistance conferred by a primary infection to the extent that they will respond to reinfection with the development of a second primary type pulmonary lesion associated with caseation of the regional lymph nodes, the result of studies all over the world have shown this event to be decidedly uncommon, regardless of the degree of exposure to infection."

[4] In discussing terminology, Terplan (Supplement to Am. Rev. Tuberc., August, 1940, page 8) advocates the term "endogenous exacerbation" for this process. [Editor]

When the present study to determine the relative frequency of death from "primary" and "reinfection" tuberculosis in adults was begun, the dogma that caseous lymph nodes were indicative of a progressive primary infection and calcified lymph nodes of a healed primary infection was accepted. On this basis alone, 62 of the 100 cases could be clearly separated into two groups: (*1*) 34 adults died from a primary tuberculous infection with the youngest being 16 years of age and the oldest being 68 years of age; (*2*) 28 adults died from a reinfection tuberculosis with a range in age from 27 to 76 years. The pattern of the disease as a whole was indistinguishable in the two groups.

The finding of both caseous and calcified lymph nodes in 17 cases was not at all anticipated. Two explanations may be offered for this. First, one primary focus may have healed and a concomitant primary focus may have progressed. This explanation hardly seems plausible for the majority of the caseous lymph nodes resembled similar nodes observed in a primary infection and in a few cases the healed primary was in the intestine, thereby necessitating concomitant primary infection in lung and intestine with a difference of behavior in the two sites in each case. The second explanation, supported by Terplan's report (12) and the author's own observation, is that, following healing of a primary infection, a reinfection was incurred which acted like a primary infection. This, in so far as the author is aware, has been reported in but 2 cases dying from tuberculosis by Terplan (7). An incidence of 17 per cent in this series is certainly not in keeping with the observation of Rich (13). Perhaps an explanation of this unexpected discovery is the thoroughness with which the lymph nodes were investigated. The pattern of tuberculous infection resembled that observed in the two groups discussed above.

The group of 21 cases in which no macroscopic evidence of caseation or calcification in the lymph nodes was found brings up the question of incomplete primary complexes, that is, a pulmonary focus without lymph node involvement. Such a condition apparently has not entered the considerations on phthisis. Terplan (14) recently has reported as high as 28 per cent of incomplete primary complexes in cases dying from causes other than tuberculosis which corresponds fairly closely to an incidence of 21 per cent in the group dying from tuberculosis observed in this study. In these cases one is in a quandary as to how to classify them. Are they cases of reinfection in which an incomplete primary complex has healed, or are they examples of progressive incomplete primary complexes? The literature on tuberculosis contains an occasional mention of incomplete primary complexes, but because of its apparent infrequency little serious consideration has been given the phenomenon. When, however, the position is taken that phthisis is a reinfection tuberculosis, as is done by Pinner,[5] Opie and

[5] Pinner, in his discussion of "Incipient Pulmonary Tuberculosis as a Direct Consequence of Late Primary Infection," ends his discussion as follows: "This whole problem of primary pulmonary tuberculosis in adults has, so far, found but little attention in U.S.A. It is entirely possible that these primary forms of pulmonary tuberculosis in adults are less frequent and less severe in this country than in some parts of Europe." (Pulmonary Tuberculosis in the Adult, 1945, page 272.) It is the belief of the author that fatal primary pulmonary tuberculosis acquired in adult life is more frequent than is generally appreciated in this country.

others, the question of incomplete primary complexes becomes very important. In this series, it involved one-fifth of the cases. Here again, the pattern of disease differed not at all from that observed in the other groups.

From the foregoing discussion, it is apparent that tuberculosis in the adult can hardly be placed in one all-inclusive group, that is, reinfection disease; or explained by a single phenomenon, that is, hypersensitivity at high tide or low ebb. Hypersensitivity may well be a *product of* rather than a *cause of* the pathological processes observed. To the author, the lack of uniformity in the cases seems to fit in very well with the way Nature works. Concepts of a disease process are enhanced by a proper integration of the variables observed, whether they be observed in natural or experimentally produced disease. Not infrequently this integration results in a realignment of accepted concepts. Such would seem to be the case in tuberculous disease in the adult for it appears that the peculiar pattern of phthisis can result from either a reinfection or a progressive primary disease.

From the data obtained from this investigation it is possible to assemble groups of cases which would either confirm or refute the divergent views now held by different authors. For instance, Blumenberg's idea that age rather than allergy influences lymph node involvement can easily be supported but a different assembly of cases would indicate that allergy might have the greater influence. It is frequently argued that the reason caseation of lymph nodes does not occur in reinfection disease is that the allergic state aids in localizing the bacilli so that they cannot gain access to the lymphatics. Contrariwise, it can be shown that, in most cases of reinfection, microscopic tuberculous foci are present in lymph nodes in the path of drainage and it can be argued that the lack of development of extensive caseation is due to unfavorable growth conditions in the lymphoid tissue.

Roentgenological studies of adults with so-called reinfection tuberculosis fail to reveal any calcified foci in the thorax in the majority of the cases. Enlarged lymph nodes, indicative of extensive caseation, are infrequently observed in adults who develop a "reinfection type" of disease after a conversion from a negative to a positive tuberculin sensitivity. The reasons for this condition are readily given. The calcified remnants of a healed primary infection are frequently too small to be recognizable roentgenologically, or are so placed that they would not be evident in the usual roentgenographic positions. The amount of caseation in lymph nodes in primary tuberculosis in the adult is very frequently too little to cause any appreciable enlargement of the nodes. It is no wonder that the most ardent supporters of the dogma that phthisis is a "reinfection" tuberculosis are unable to differentiate roentgenologically between a primary and a reinfection disease in the adult.

Opie (1) and Terplan (7) are advocates of roentgenograms of excised lungs in studies such as the one under discussion. The author agrees that small calcified foci, especially in the lung, may be more quickly and easily detected by roentgenograms but small foci of caseation and of fibrosis will fail to be registered in the films. It would be most unfortunate to have the roentgenogram replace experienced sight and trained palpation in the examination of fresh tissues. If the

roentgenograms of excised lungs are utilized there still remains the necessity for very thorough dissection to reveal small foci not visualized in the roentgenograms.

A fairly definite idea of the location of the oldest cavity was possible in the majority of the cases and, with one exception, the location was in the upper portions of pulmonary lobes. In the exception, the small cavity was in the diaphragmatic portion of a lower lobe. The cases showed the usual and peculiar pattern of phthisis. This occurred in both primary and reinfection cases, provided it was possible to establish on morphological grounds a distinction between primary and reinfection disease. It would seem that entirely too much emphasis has been placed upon *reinfection* as THE cause of phthisis.

That a large majority of individuals localize and heal primary tuberculous infections is evident from the frequent calcified primary complexes found at necropsy. It is probable that many reinfections are also similarly handled although proof of this is not so readily obtained. Apparently the factors which permit the development of a progressive disease are peculiarities of certain areas of lung tissue and of conditions within an individaual which to date have escaped detection. One evident fact is that an ability to heal a first infection is no guarantee that a subsequent infection will be similarly controlled. Whenever tuberculous foci in upper portions of pulmonary lobes progress to the state that they assume clinical significance, which includes the early indistinct roentgenographic shadows of "minimal" disease, the condition is of serious import irrespective of whether it is a primary or a reinfection lesion, and also irrespective of the age of the adult. It would seem advisable to relegate the present concept of phthisis as a "reinfection" disease to a place of lesser importance for by no means can it explain all cases of progressive disease in adults.

CONCLUSIONS

1. An analysis of 100 adults dying from tuberculosis is presented with reference to the incidence of "primary" and "reinfection" disease on the dogma that caseous nodes indicate a progressive primary infection and calcification in lymph nodes a healed primary infection. In this connection, the term reinfection is used in the sense that a previous infection had been healed.

2. Thirty-four per cent of the cases died from a primary infection. Twenty-eight per cent of the cases died from a reinfection. Seventeen per cent had both calcified and caseous nodes and may be interpreted as dying from a reinfection disease which acted like a primary infection. Twenty-one per cent of the cases had neither caseous nor calcified nodes. They may be regarded as dying from (*1*) a progressive incomplete primary complex tuberculosis or (*2*) a reinfection disease in which an incomplete primary complex had healed.

3. The pattern peculiar to phthisis was present in these cases irrespective of the conditions observed in the lymph nodes.

4. It is evident that all cases of progressive pulmonary tuberculosis in the adult cannot be explained on the basis of a reinfection, and it would appear to be equally difficult to explain them on the generally accepted interpretation of the influence of hypersensitivity in reinfection.

5. For the development of progressive pulmonary tuberculosis, that is, phthisis in the adult, it is essential that the tubercle bacillus become lodged in the cephalic portions of pulmonary lobes whether it be a first or a subsequent infection. Beyond this fact all explanations are nebulous and await clarification.

CONCLUSIONES

La Incidencia de la Tuberculosis Primaria y de Reinfección como Causa de Muerte en el Adulto

1. Este análisis de 100 personas adultas que murieron de tuberculosis preséntase con referencia a la incidencia de enfermedad "primaria" y de "reinfección", a base de la teoría de que los ganglios caseosos indican infección primaria evolutiva y los calcificados infección primaria cicatrizada, usándose el término de reinfección en el sentido de que una infección previa ha cicatrizado.

2. Un 34 por ciento de los enfermos murieron de una infección primaria, y un 28 por ciento de una reinfección. Un 17 por ciento tenían tanto ganglios calcificados como caseosos, pudiendo interpretarse la muerte como debida a una reinfección que actuó como infección primaria. En 21 por ciento de los casos no había ganglios caseosos ni calcificados, y la muerte puede considerarse como debida a: (*1*) una tuberculosis compleja primaria incompleta evolutiva o (*2*) una enfermedad tipo reinfección después de haber curado un complejo primario incompleto.

3. Independiente del estado observado en los ganglios linfáticos, en estos casos existía el patrón peculiar de la tisis.

4. Es manifiesto que no pueden explicarse a base de reinfección todos los casos de tuberculosis pulmonar evolutiva en el adulto, y parece igualmente difícil explicarlos tomando la interpretación aceptada generalmente del influjo de la hipersensibilidad en la reinfección.

5. Para el desarrollo de la tuberculosis pulmonar evolutiva, es decir, tisis, en el adulto es indispensable que el bacilo tuberculoso se aloje en las porciones cefálicas de los lóbulos pulmonares ya se trate de infección primaria o subsiguiente. A partir de ahí todas las explicaciones resultan nebulosas y necesitan esclaracimiento.

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STREPTOMYCIN SENSITIVITY OF TUBERCLE BACILLI[1]

Studies on Recently Isolated Tubercle Bacilli and the Development of Resistance to Streptomycin *in vivo*

GUY P. YOUMANS[2] AND ALFRED G. KARLSON[3]

Using the H37 strain of *Mycobacterium tuberculosis*, Schatz and Waksman (1) first demonstrated that tubercle bacilli were susceptible *in vitro* to the bacteriostatic action of streptomycin. Subsequently, Youmans (2) discovered that the growth of 5 additional strains of virulent, human type tubercle bacilli was decidedly inhibited *in vitro* by streptomycin. Feldman, Hinshaw and Mann (3) have proved that streptomycin has a marked suppressive action on experimental tuberculosis of guinea pigs, and Youmans and McCarter (4) have found this agent effective in the control of experimental tuberculosis of white mice.

It has been noted that with other bacteria (5) there is considerable variation in sensitivity to streptomycin between different strains of the same species. For this reason it was advisable to determine not only the sensitivity of strains of tubercle bacilli isolated from patients before treatment with streptomycin was started but also the range of sensitivity to streptomycin likely to be encountered among recently isolated strains of tubercle bacilli. The relative sensitivity of human, bovine and avian strains of tubercle bacilli to streptomycin was also determined.

In a preliminary communication by Youmans, Williston, Feldman and Hinshaw (6) it was reported that tubercle bacilli became resistant when exposed to streptomycin either *in vivo* or *in vitro*. The present paper reports further observations on the development of resistance to streptomycin by tubercle bacilli, isolated from patients who were undergoing treatment with this agent.

Observations on the development of resistance to streptomycin *in vitro* will be reported in a separate communication.

METHODS

Isolation of the strains of tubercle bacilli were made chiefly from a large number of patients who were suffering from various clinical types of tuberculosis; a few specimens were obtained at necropsy. Specimens of sputum and gastric washings from each patient were mixed with an equal volume of 3 per cent solution of sodium hydroxide, shaken in a Kahn shaker for fifteen minutes and placed in an incubator at 37°C. for thirty minutes. The mixture was then neutralized with 8.7 per cent solution of hydrochloric acid and centrifuged. The sediment was transferred to four tubes of glycerinated egg-yolk agar and four tubes of egg-yolk agar which contained no glycerine.[4] Urine and suspensions

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[4] Nonglycerinated medium, as well as that which contains glycerine, is used in the culture of all specimens from new patients to facilitate the isolation of any bovine strains, since bovine strains do not grow well, on original isolation, in the presence of glycerine.

of tissues were treated with oxalic acid according to the method of Corper and Uyei (7) and cultures were made in the manner just described.

Cultures were examined weekly. Selections for tests of sensitivity to streptomycin were made when colonies were large enough to be scraped off and placed in suspension, usually after three to six weeks of incubation.

The sensitivity of the strains to the bacteriostatic action of streptomycin was determined by a modification of the method previously described (2–7). This method, in detail, is as follows:

A modified Proskauer and Beck synthetic medium of the following composition was employed:

Asparagin	0.5 per cent
Monopotassium phosphate	0.5 per cent
Potassium sulfate	0.05 per cent
Glycerol	2.0 per cent

The above ingredients are dissolved in the order given in distilled water, care being taken that each ingredient is completely dissolved before the next is added. The hydrogen ion concentration is then adjusted to pH 7.0 with 40 per cent sodium hydroxide, then add:

Magnesium citrate 0.15 per cent

This constitutes the basic medium which is sterilized in the autoclave at 15 lbs. pressure for twenty minutes. To this medium is then added aseptically, for the purpose of obtaining more rapid growth, enough sterile human, bovine or horse plasma or serum to make a final concentration in the medium of 10.0 per cent. The plasma or serum is sterilized by filtration through a Berkefeld or other suitable bacteriological filter.

Glassware: All glassware, tubes, flasks, pipettes, etc., should be thoroughly cleaned with either soap and water or cleaning solution and rinsed seven to eight times with tap water and three to four times with distilled water.

Test tubes of any size may be employed, but care must be taken to adjust the volume of medium per tube to the size of the test tube. The maximum volume of medium used in test tubes 200 x 25 mm. is 10.0 ml. In test tubes 150 x 20 mm. the volume should not exceed 5.0 ml. Smaller volumes can be used to advantage. One of us (A.G.K.) employed 4.0 ml. volumes in 15 x 150 mm. test tubes. All glassware, including pipettes, is sterilized in the autoclave at a pressure of 20 lbs. for twenty minutes.

Streptomycin dilutions: Streptomycin[5] is dissolved aseptically in the above medium in whatever concentration may be desired. We routinely employ twofold dilutions which range from 100 micrograms per ml. to 0.095 micrograms per ml. Higher concentrations are employed as needed. When preparing serial dilutions it is important to use separate pipettes for each dilution. Otherwise, not only will the dilutions be inaccurate but, due to carry over, inhibition of growth may occur several tubes lower than it should.

Since we have found that the potency of streptomycin was not lost even when the medium in which it was contained was stored in the refrigerator at 10°C. for as long as five weeks, it is economical to prepare as many as a hundred tubes of each concentration of streptomycin at one time and store them for future use.

[5] Furnished to A. G. K. through the courtesy of Merck & Co., Rahway, New Jersey. Furnished to G. P. Y. through the courtesy of Dr. L. A. Sweet, Parke, Davis & Company, Detroit, Michigan.

Preparation of suspensions of tubercle bacilli: A few flakes of growth of the tubercle bacillus strain to be tested are placed in one drop of 0.01 molar phosphate buffer or medium in the bottom of a sterile mortar. These are ground by hand for a few minutes until a relatively homogeneous suspension is obtained. This is diluted to a volume of 5 to 15 ml. by the gradual addition of sterile buffer solution. The resulting suspension is then transferred to a sterile test tube and allowed to stand for thirty minutes. The larger coarse clumps will settle out leaving a relatively fine homogeneous supernatant suspension. This supernatant suspension is transferred by decantation or aspiration to a sterile test tube. Ten to 15 such suspensions can easily be prepared in an hour.

These suspensions may be standardized in several ways. Since a tenfold variation in the amount of inoculum will not affect the endpoints of streptomycin sensitivity, an accurate standardization is not necessary. However, an inoculum should be chosen that will give good growth in a relatively short time and yet not be so large that false growth readings will be made.

The best, and most rapid, method of standardization is the use of turbidimetric measurements in any suitable photoelectric colorimeter.

If such an instrument is not available, use of Hopkins vaccine centrifuge tubes is rapid and not laborious. An aliquot of 1 to 5 ml. of each suspension is transferred to a Hopkins vaccine centrifuge tube and centrifuged at high speed for thirty minutes. The packed tubercle bacilli in the tip of the tube are measured in terms of cubic millimeters and arbitrarily each cubic millimeter is assigned a wet weight of 1.0 milligram.

After standardization the suspensions are diluted so as to contain the desired inoculum for each tube in 0.1 or 0.2 ml. of phosphate buffer or medium. The inoculum to be preferred should be from 0.1 to 0.5 mg. for each tube (wet weight Hopkins tube value).

Duplicate tubes of each streptomycin dilution and appropriate control tubes of medium are inoculated with 0.1 or 0.2 ml. containing the desired amount of tubercle bacilli. The tubes should be inoculated rapidly to minimize the settling out of tubercle bacilli in the pipette. The tubes should be shaken vigorously after being inoculated and then incubated at 37°C.

Growth of tubercle bacilli will frequently be evident as early as two to three days and final readings can often be made as early as four to five days after inoculation. However, since larger amounts of growth are easier to observe, we have found that an incubation period of seven to fourteen days is the most satisfactory before making the final reading.

In this medium the tubercle bacilli grow at the bottom and up the sides of the tube leaving the supernatant clear. When the tubes are gently shaken flakes of tubercle bacilli swirl through the medium. This flaky type of growth is very characteristic and with a little experience is readily distinguished from any contaminating organism.

The least amount of streptomycin which completely prevents this subsurface (submerged, deep-seated) growth is recorded as the streptomycin sensitivity of the strain being tested.

The reliability of the method described for determining the sensitivity of tubercle bacilli to streptomycin is such that no significant differences were obtained when the same strains were tested independently in separate laboratories. Duplicate tests and repeated examinations of the same cultures for several months gave similar results. The variation was never greater than a plus or minus one dilution; the inherent error of the method.

RESULTS

In table 1 are tabulated the results on the tests of 131 recently isolated strains of tubercle bacilli for sensitivity to streptomycin. Those strains were, culturally,

tubercle bacilli of human type; animal typing tests for pathogenicity were not done. The results show that a majority of the strains were highly sensitive to the bacteriostatic action of streptomycin: 90 per cent of them were inhibited by a concentration of less than 2 micrograms of streptomycin per cc. of medium. None of the strains exhibited an extremely high natural resistance to streptomycin. All of these strains were obtained from patients prior to treatment with streptomycin.

TABLE 1

Sensitivity of 131 recently isolated human strains of tubercle bacilli to streptomycin

STRAINS (131)	EFFECTIVE CONCENTRATION OF STREPTOMYCIN, MICROGAMS PER ML.
6	0.095
26	0.19
44	0.39
26	0.78
16	1.56
9	3.12
3	6.25
1	12.5

TABLE 2

Sensitivity of 16 bovine and 14 avian strains of tubercle bacilli to streptomycin

BOVINE STRAINS (16)	EFFECTIVE CONCENTRATION OF STREPTOMYCIN, MICROGRAMS PER ML.
3	0.095
5	0.19
4	0.39
2	0.78
1	1.56
1	3.12
AVIAN STRAINS (14)	
1	0.39
2	1.56
5	3.12
2	6.25
3	25.0
1	50.0

In table 2 are reported the results of tests of 16 known bovine and 14 known avian strains of tubercle bacilli for sensitivity to streptomycin. The degree of sensitivity of bovine strains appears to be of about the same order as that of human strains. A majority of the avian strains appear to have greater natural resistance to the bacteriostatic action of streptomycin than do human or bovine strains.

TABLE 3

Sensitivity to streptomycin of tubercle bacilli isolated from patients during treatment with streptomycin

CASE NUMBER	SOURCE OF ORGANISMS	STREPTOMYCIN			
		Days administered	Average daily dose, mg.	Total administered, g.	Effective concentration, micrograms per ml.
1	Urine	29	0.1 to 0.2	3.6	3.12
1	Urine	71	0.5 to 1.0	61.1	1,000.0
2	Guinea pig* spleen	92	2 to 4	238.0	>1,000.0
3	Draining craniotomy wound	38	0.5	19.0	3.12
4	Gastric contents	56	1.5	84.0	>1,000.0
5	Urine	0	0	0	0.095
5	Kidney†	38	0.5 to 1.0	30.7	100.0
6	Gastric contents	0	0	0	0.39
6	Gastric contents	131	1 to 2	192.0	>2,500.00
7	Spinal fluid	0	0	0	0.78
7	Meninges‡	48	1 to 2	58.1	500.0
8	Gastric contents	0	0	0	0.78
8	Gastric contents	78	1.0	78.0	>2,000.0
9	Gastric contents	0	0	0	0.78
9	Gastric contents	131	1 to 3	261.0	>2,000.0
10	Axillary abscess	36	1.0	31§	0.095
11	Sputum	30	1.7	51.0	0.39
12	Spinal fluid	88	2.5	220.0	10.0
13	Lung‡	42	0.5 to 10.0	242.5	1.56
14	Gastric contents	30	3.0	90.0	0.39
14	Gastric contents	60	3.0	180.0	>2,000.0
15	Urine	34	1.8	61.2	0.39
15	Urine	46	1.8	82.8	>2,500.0

* Inoculated with urine from patient.
† Surgical specimen.
‡ Specimen obtained at necropsy.
§ Patient received less than 1 g. on a few days.

In table 3 are presented the results of tests for sensitivity to streptomycin made on cultures of tubercle bacilli isolated from patients during the course of

treatment with streptomycin. In addition, in cases 5, 6, 7, 8 and 9 the results of tests for sensitivity to streptomycin made on strains isolated prior to treatment are also given; these results, along with others, were also used in preparation of the data presented in table 1.

The data presented in table 3 are not complete enough to warrant conclusions as to clinical significance but certain facts are apparent. Cultures isolated from patients who have been given 1 to 2 g. of streptomycin daily for several months may have much greater resistance to the drug *in vitro* than cultures isolated prior to treatment. Whether this increase in resistance to the drug is gradually acquired by the tubercle bacilli or appears suddenly as a result of survival of resistant strains normally present is not discernible from our data. Of special interest in this regard is case 15 in which tubercle bacilli in cultures of urine obtained thirty-four days after treatment was started were sensitive to streptomycin in concentration of 0.39 micrograms per cc., whereas tubercle bacilli in cultures obtained twelve days later were resistant to the substance in concentration of more than 2,500 micrograms per cc.

The method used for determining the sensitivity of tubercle bacilli to streptomycin permits detection of only those bacilli which have the greatest resistance to the drug; such bacilli are detected even though they may be present in a culture in exceedingly small numbers. We have not determined whether or not both sensitive and resistant strains may be present in the same cultures.[6] At present we do not know what clinical significance may be attached to the presence of streptomycin-resistant strains of tubercle bacilli in treated patients.

CONCLUSIONS

The majority of tubercle bacilli isolated from patients prior to treatment with streptomycin are sensitive *in vitro* to streptomycin in concentrations of less than 2 micrograms per ml. of medium. Ninety per cent of 131 strains studied were inhibited by the drug in concentration of 1.56 micrograms or less per ml. of a liquid medium which contained 10 per cent horse, beef or human plasma.

Bovine strains of tubercle bacilli apparently exhibit the same order of sensitivity to streptomycin as those of the human type.

Avian strains of tubercle bacilli are somewhat more resistant to the action of streptomycin *in vitro* than are mammalian strains.

Cultures of tubercle bacilli isolated from patients after several months or more of treatment with streptomycin exhibit resistance to streptomycin *in vitro* several thousand times as great as that of cultures isolated prior to treatment.

The clinical significance of the resistance to streptomycin developed by tubercle bacilli is not definitely established.

CONCLUSIONES

Sensibilidad de los Bacilos Tuberculosos a la Estreptomicina

La mayoría de los bacilos tuberculosos aislados de los enfermos antes de recibir la estreptomicinoterapia son sensibles *in vitro* a la estreptomicina a concentra-

[6] This phase of the question is now under investigation in the laboratory of one of us (A. G. K.).

ciones de menos de 2 microgramos por ml. de medio. Noventa por ciento de 131 cepas estudiadas fueron inhibidas por la droga a una concentración de 1.56 microgramos o menos por ml. de un medio líquido que contenía 10 por ciento de plasma equino, bovino a humano.

Las cepas bovinas de los bacilos tuberculosos manifiestan aparentemente el mismo tenor de sensibilidad a la estreptomicina que las del tipo humano.

Las cepas aviarias son algo más resistentes a la acción de la estreptomicina *in vitro* que las de mamífero.

Los cultivos de bacilos tuberculosos aislados de enfermos tratados por varios meses con estreptomicina manifiestan una resistencia *in vitro* a la estreptomicina varios miles de veces mayor que los cultivos aislados antes del tratamiento.

No se ha establecido definitivamente el significado clínico de la resistencia a la estreptomicina desarrollada por los bacilos tuberculosos.

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STREPTOMYCIN RESISTANT STRAINS OF TUBERCLE BACILLI[1,2,3]

Production of Streptomycin Resistance *in vitro*

ELIZABETH H. WILLISTON AND GUY P. YOUMANS

That the sensitivity of bacteria to certain antibiotics can be altered by continued exposure both *in vivo* and *in vitro* has been shown by many investigators. The publications of Selbie, Simon and McIntosh (1) and of Gallardo (2) and others report the appearance of penicillin-resistant strains of *Staphylococcus aureus* in patients treated with penicillin. Resistance to penicillin has also been produced *in vitro*. In this connection Abraham, Chain and collaborators (3), McKee and Houck (4), Rantz, Lowell and Kirby (5), Rammelkamp and Maxon (6), and others have succeeded in producing penicillin-resistant strains of a number of pathogenic bacteria by repeated exposure in broth cultures to increasingly higher concentrations of the drug.

Buggs, Bronstein and associates (7) reported in 1946 that streptomycin-resistant strains had been isolated from patients receiving treatment with that drug. *Staphylococcus albus*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, alpha hemolytic streptococci, diphtheroids and possibly *Aerobacter aerogenes* and beta hemolytic streptococci were shown to develop such resistance in the patient. Streptomycin resistance was induced *in vitro* in 4 strains of gonococcus and 9 strains of meningococcus by Miller and Bohnhoff (8).

In a preliminary report Youmans, Williston, Feldman and Hinshaw (9) showed that some strains of tubercle bacilli isolated from patients under streptomycin treatment showed a marked resistance, indicating that this organism is not an exception in its response to repeated exposure to the drug in the patient. At this time, 2 strains of *Mycobacterium tuberculosis* had been exposed to streptomycin *in vitro* and had developed an increase in resistance of over a thousandfold. The present paper details the results obtained following exposure of 18 strains of *M. tuberculosis* to streptomycin *in vitro*.

METHODS

The cultures used were avian, bovine and human strains[4] including the standard H37-Rv. The human and bovine strains had been isolated recently from patients with active tuberculosis who, with 2 exceptions (cases 6 and 97), had had no streptomycin therapy previous to culturing.

Synthetic medium containing plasma and streptomycin was prepared as described by

[1] From the Department of Bacteriology, Northwestern University Medical School, Chicago, Illinois.

[2] This work was aided by a research grant from Parke, Davis & Company, Detroit, Michigan.

[3] Streptomycin was furnished through the courtesy of Dr. L. A. Sweet, Parke, Davis & Company, Detroit, Michigan.

[4] Strains used are included in the article reported by G. P. Youmans and A. G. Karlson on page 529 in this journal.

Youmans (10, 11). This was tubed in 5 ml. amounts in test tubes 20 by 150 mm. Suspensions of the tubercle bacilli selected for exposure were made in .01 molar potassium phosphate buffer at pH 7.0 and 0.25 mg. of these suspensions served as the inoculum for each tube. The streptomycin dilutions ranged from 1,000 micrograms to 0.095 micrograms per ml. and consisted of 13 different dilutions. Exposing the culture each time in all dilutions served both to make the exposure and to measure the amount of resistance developed. At one- to two-week intervals transfer was made from the tube showing growth and containing the greatest amount of streptomycin.

Two methods were used for this reëxposure of a given strain to streptomycin. In one, the bacteria from the streptomycin tubes were planted on egg medium and incubated till the growth was abundant enough to grind and resuspend for a further exposure. In the second method the organisms from the tube with the most streptomycin showing growth were used as inoculum for all the tubes of the next exposure. Neither method showed any consistent advantage over the other.

At intervals comparative tests using the parent strain of the test organism were run. A test of the potency of the streptomycin dilutions was made by planting the H37Rv strain in a series of dilutions from each batch of medium used. Within the limit of error of the method this strain was inhibited by the same amount of streptomycin each time.

RESULTS

Nine strains of *M. tuberculosis* (7 human, one avian and one bovine) developed at least a thousandfold resistance to streptomycin (table 1). The time of exposure varied from 52 to 120 days. Nine other strains (one bovine) showed somewhat less increase of resistance when exposed from 66 to 117 days. Of these last, 3 developed only a fourfold resistance and one developed only a twofold resistance after eighty-five days.

Table 1 shows the total time in days each culture was incubated in the presence of streptomycin. In view of the fact that the streptomycin slowly decreases in potency during incubation, these figures do not indicate the true concentration of streptomycin.

The rate at which the resistance to streptomycin increased followed no particular pattern, at least so far as the method used could detect. Some cultures showed a rather steady increase in the amount of streptomycin they could withstand in successive culture generations; others made little progress in three or four culture generations and then suddenly increased markedly in resistance.

As has been noted previously by Youmans (10), nonresistant strains of *M. tuberculosis* in the synthetic medium plus plasma gave a rather sharp line of demarcation between the dilutions which inhibited and those which did not inhibit. Some strains which had been exposed to streptomycin for several generations showed a tendency to "taper off," to give slight growth in 4 or 5 dilutions more potent than the one which permitted abundant growth.

After a strain had become resistant to 1,000 micrograms it was planted on Herrold's egg agar slant and tested from time to time to detect any loss of this property. One strain, H37Rv, was observed for eleven months and failed to show any loss of resistance. The other strains showed no marked change of resistance after four to six months.

One ml. amounts of a filtrate of a culture of resistant H37Rv were added to a dilution series of streptomycin in broth and plasma and inoculated with a sensitive strain of H37Rv. The streptomycin showed no lack of potency in the presence of the filtrate.

TABLE 1

Streptomycin resistance developed in vitro of strains of M. tuberculosis

STRAIN AND TYPE	SOURCE	LEAST AMOUNT OF STREPTOMYCIN IN MICROGRAMS PER ML. REQUIRED TO INHIBIT COMPLETELY GROWTH OF ORIGINAL CULTURE	STREPTOMYCIN RESPONSE AFTER EXPOSURE (MICROGRAMS PER ML.)	TOTAL NUMBER OF DAYS EXPOSED
Human				
1	Sputum	0.195	>1000	94
23	Gastric washing	0.78	>1000	96
24	Gastric washing	0.19	>1000	86
52	Gastric washing	3.125	>1000	57
60	Lymph node	0.095	>1000	91
100	Gastric washing	1.56	>1000	120
Bovine				
69	Urine	0.095	>1000	99
Avian				
40	Stock culture	3.12	>3200	52
Human				
H37Rv		0.78	>1000	63
H37Rv		0.78	>1000	56
6	Urine	3.12	12.5	98
15	Gastric washing	0.78	3.125	66
20	Gastric washing	0.78	50.0	100
21	Gastric washing	0.39	3.125	77
97		1.56	500.0	112
110	Cervical lymph nodes	0.78	500.0	108
117		1.56	12.5	92
120	Sputum	1.56	3.125	85
Bovine				
118	Urine	0.39	1.56	117

Patients from whom 7 of the strains were isolated subsequently received streptomycin and eventually developed streptomycin resistant strains *in vivo* (strains 24, 100, 69, 6, 15, 20, 118 (table 1)).

SUMMARY

Fourteen out of 18 strains of *M. tuberculosis* developed definite resistance to streptomycin when cultured for successive generations in synthetic broth with plasma and streptomycin. Three strains showed only a fourfold increase in resistance, and one only twofold. There was a wide variation in the rate at

which the resistance developed. Nine strains showed at least a thousandfold increase in resistance after from 52 to 120 days' exposure; other strains showed less increase of resistance. Resistance was maintained for as long as eleven months.

SUMARIO

Cepas Estreptomicino-resistentes de los Bacilos Tuberculosos

Catorce de 18 cepas del *M. tuberculosis* mostraron resistencia bien definida a la estreptomicina después de ser cultivados durante generaciones sucesivas en caldo sintético con plasma y estreptomicina. Tres cepas sólo cuadruplicaron su resistencia, y una sólo la dobló. Varió sumamente la rapidez con que se desarrolló la resistencia. Nueve cepas revelaron un aumento por lo menos de mil en su resistencia al cabo de una exposición de 52 a 120 días; otras revelaron menos aumento. La resistencia se mantuvo hasta once meses.

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THE EFFECT OF GLYCEROL AND RELATED SUBSTANCES ON THE GROWTH AND THE OXYGEN UPTAKE OF THE TUBERCLE BACILLUS[1, 2]

HUBERT BLOCH, E. MATTER AND EMANUEL SUTER

Glycerol is known to play a particular part among the nutrients in the culture of *M. tuberculosis* in synthetic media. For most strains, glycerol is the best or even the only usable source of carbon. On the other hand, if tested in the Warburg apparatus as substrate for bacterial cell metabolism, there are many respiration-promoting compounds with much more intensive effects than glycerol, belonging to various chemical groups, for example, aliphatic acids and alcohols, derivatives of benzoic acid, carbohydrates, etc. There does not seem to exist any direct relation between the growth- and the respiration-promoting faculty of a substance. On the contrary, a respiration-promoting substance can promote as well as inhibit bacterial growth, or even be without any influence on it (Bloch, 1942). Considering these facts it is not surprising that the respiratory effect of glycerol does not correspond to its outstanding growth-promoting ability. However, it was promising to compare the action of glycerol with that of chemically related compounds, with the aim of gaining a better understanding of the structural properties of substances, necessary, if they are to act both as respiratory stimuli and as growth-promoting compounds.

MATERIALS

We used the following substances for our experiments:

(I) *Natural glycerol.*

(II) *Synthetic glycerol:* Prepared from isopropylalcohol according to Bloch, Erlenmeyer and Furger (1944).

(III) *α-monoacetylglycerol:* From acetyl-acetone-glycerol according to Fischer and Pfähler (1920).

(IV) *α-α′-diacetylglycerol:* From glycerol and glacial acetic acid (Seelig, 1891; Geitel, 1897; Wegschneider, 1913).

(V) *Triacetylglycerol:* From glycerol and acetic anhydride (DRP 347 897; Friedländer, *14*, 159, 1921).

(VI) *Acetone glycerol:* Prepared according to Fischer (1895).

(VII) *C-methyl glycerol:* From crotyl alcohol and HOCl by saponification with NaOH (Batalin and coworkers, 1937; Delaby, 1922). The compound is prepared, therefore, like II, not from glycerol, but by purely synthetic methods.

(VIII) *Glycerol-α-monomethylether:* From Na methylate and glycerol monochlorhydrine (Grün and Bockisch, 1908).

(IX) *Glycerol-α-monoisoamylether:* Prepared by pouring α-monochlorhydrine through a dropping funnel into a boiling 2 per cent solution of isoamyl Na-alcoholate in isoamyl alcohol. BP_{14}: 130–132°C.

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[2] Studies on the metabolism of tubercle bacilli, No. IX.

(X) *α-α-diglycerolether:* $CH_2OH \cdot CHOH \cdot CH_2—O—CH_2 \cdot CHOH \cdot CH_2OH$ Preparation: 400 g. polyglycerol (prepared by heating glycerol with 1 per cent NaOH to 250°C.); 1,500 g. acetone; 10 cc. concentrated HCl, six hours at 30°C., while stirring. The polyglycerol dissolves only partially. Neutralize with dry Na_2CO_3, filter and distill. Dissolve the fraction 120–200°C. (14 mm.) in water and extract the diacetone-diglycerol ether with ether. BP_{14}: 138–140°C., yield 31 g. Dilute with 30 cc. water and keep for two hours at 50–60°C. after adding one drop concentrated H_2SO_4. Neutralize with $BaCO_3$, distill off the acetone, filter and distill. BP_{14}: 255–257°C., yield 13 g.

To prepare diglycerol of undetermined configuration (ethers α- α; -β, β-β), see also Wright and du Puis (1946).

(XI) *3-aminopropane diol (1,2):* From glycide and ammonia (Knorr and Knorr, 1899).

(XI & XII) *Mono- and diacetone glucose:* Prepared according to Bell (1935).

We have, then—excepting the last two—differently substituted derivatives of glycerol which in their physical properties are very closely related to glycerol itself (colorless, water-clear, viscous liquids which can easily be mixed with water). The two acetone compounds of glucose have been chosen because glucose represents the only compound that could replace in our previous experiments glycerol in the culture medium with no ill effects (Bloch, 1942). We experimented with the synthetically prepared glycerol to exclude any impurities in the natural glycerol.

For the following experiments, the compounds were dissolved, buffered and neutralized.

BACILLI

The strain used was of human type and highly virulent for guinea pigs. Bacilli were grown on a synthetic medium of the following composition:
Ten to 14-day-old cultures were used.

NaH_2PO_4	3 g.
KH_2PO_4	4 g.
$MgSO_4$	2.5 g.
Sodium citrate	2.5 g.
Ferrous ammonium sulphate	0.01 g.
Glycine	5 g.
Glycerol	25 g.

Distilled water add 1,000 cc.
pH adjusted to 7.0.

METHODS

Respiration Experiments

Bacilli were filtered through paper (Whatman No. 5), thoroughly washed on the filter, suspended in distilled water and centrifuged at 3000 r.p.m. for fifteen minutes; this was repeated three times. The bacillary mass was then homogeneously resuspended in 0.06 M phosphate buffer pH 6.8 to make approximately 5 mg. dry weight of bacilli per cc. One cc. of this suspension was filled into each Warburg vessel, the total volume being 2 cc. + 0.2 cc. potassium hydroxide.

Temperature of the thermostate was 37.0° C. Gas used was oxygen. The respiration of the buffer-suspended bacilli in the absence of any nutrient served as control. Glycerol-promoted respiration was measured in every experiment, glycerol being added in a concentration of 0.2 Mol/1. When combined with glycerol, different compounds increased the Q_{O_2} produced by this substance and gave thus an additional effect. As we showed in a previous paper (Bloch, 1944), the Q_{O_2} produced by glycerol is to a large extent unaffected by the concentration of glycerol, so that an additional effect points to two separate and independent respiration mechanisms.

Growth Experiments

The compounds to be tested were added to the culture medium to replace glycerol; 50 cc. of culture medium (without glycerol) were filled into 200 cc. Erlenmeyer flasks and incubated from three to five weeks at 37° C.; the cultures were then filtered through paper, dried *in vacuo* and weighed. Our results are based on the average weight of at least three parallel flasks.

RESULTS

Respiration Experiments

(*1*) *Natural and synthetic glycerol:* No difference in the action of the two compounds on the respiration of tubercle bacilli can be seen. Both substances increase the oxygen uptake by 94 ± 5.75 per cent (average of 35 experiments). The relative increase depends on how intensively the bacteria were washed, as the maximum absolute value reached with glycerol is constant. The values to be compared must thus be based on experiments with bacilli that have passed through the same washings.

The oxygen consumption is of linear type during an experiment of six hours. Since the lag phase of *M. tuberculosis* is five to eight days, a bacillary multiplication cannot be expected during the short time of the experiment.

We found glycerol respiration to be independent of the acidity of the medium within a range of from pH 3 to 7, a fact already mentioned by Loebel, Shorr and Richardson in 1933.

(*2*) *Esters of glycerol:* The respiratory effect of the three esters of glycerol with acetic acid, that is, mono-, di- and triacetylglycerol, was investigated. If the respiration of tubercle bacilli is measured in different solutions of those esters in 0.06 M phosphate buffer pH 6.8, we find a considerable increase of oxygen uptake dependent on the concentration of the substrates (table 1). A characteristic experiment is presented in chart 1, from which two different facts appear:

(*a*) Unlike glycerol, with which the respiratory quotient is almost independent of concentration, we find in the case of glycerol esters for each compound a definite and characteristic optimum.

(*b*) The increase of the oxygen uptake produced by glycerol is considerably surpassed by that of glycerol esters. However, a combination of glycerol and glycerol esters does not produce an additional increase of respiration.

The question arose whether the glycerol esters are consumed as compound or

TABLE 1

The effect of various concentrations of mono-, di- and triacetylglycerol upon the oxygen uptake of tubercle bacilli

CONCENTRATION	PER CENT INCREASE OF OXYGEN UPTAKE EFFECTED BY		
	Monoacetylglycerol	Diacetylglycerol	Triacetylglycerol
Mol/l.			
0.5	206	38	14
0.166	400	161	129
0.14	*428*		
0.066		*456*	430
0.055	308	388	
0.05		346	440
0.033			*480*
0.025			398
0.022			390
0.018	200	211	246
0.006	119	132	152

Note: The average increase effected by glycerol from 0.5 to 0.01 M was 94 ± 5.75 per cent.

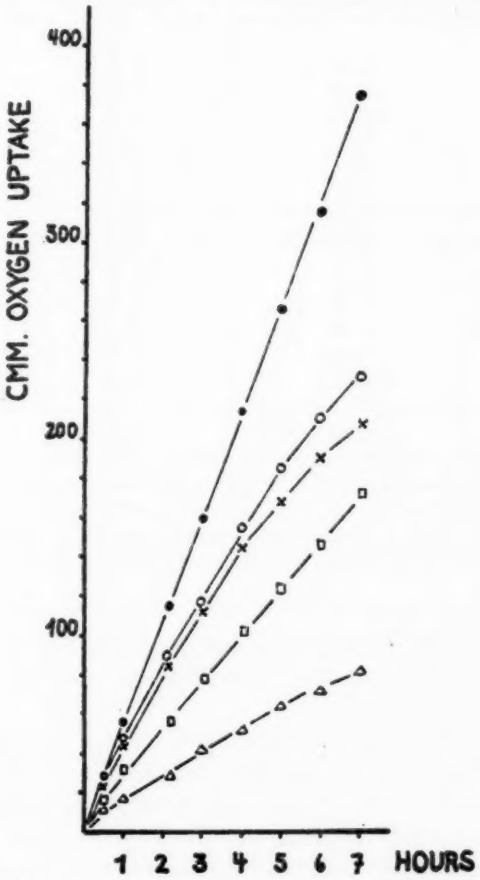

CHART 1. The effect of 0.2 Mol/l. of glycerol and of mono-, di- and triacetylglycerol upon the oxygen uptake of tubercle bacilli.

●——●: Monoacetylglycerol.
○——○: Diacetylglycerol.
×——×: Triacetylglycerol.
□——□: Glycerol.
△——△: Control.

whether they are split, so that the ester parts, that is, glycerol and acetic acid, are utilized separately. Tubercle bacilli are known to contain esterases (for references see Michaelis and Nakahara, 1923). We showed their activity by shaking equal quantities of bacilli in 0.2 M solutions of the different esters and titrating the resulting acetic acid with 0.1 n NaOH, using phenolphthaleine as indicator (table 2).

Moreover it is possible to show the esterase activity by the method of Rona and Lasnitzki (1924) in the Warburg apparatus, using a suspension of intact bacilli as well as cell-free extracts prepared by our method previously described

TABLE 2

The effect of the esterase of tubercle bacilli upon mono-, di- and triacetylglycerol

TIME	cc. 0.1 n NaOH		
	Monoacetylglycerol	Diacetylglycerol	Triacetylglycerol
minutes			
5	0.23	0.26	0.37
10	0.20	0.28	0.35
15	0.22	0.29	0.38
20	0.18	0.28	0.42
25	0.22	0.42	0.55
30	0.22	0.32	0.38
35	0.20	0.30	0.37
40	0.20	0.28	0.40
50	0.25	0.38	0.48
55	0.16	0.30	0.40
65	0.23	0.40	0.52
75	0.20	0.41	0.53
85	0.30	0.51	0.55
Total.....	2.81	4.45	5.70

Concentration of the substrates: 0.2 M, in a total amount of 50 cc. of distilled water. Temperature: 37° C. Titration with 0.1 n NaOH, with phenolphthalein as indicator. Enzyme preparation: 136 mg. (dry weight) bacilli per 50 cc. substrate solution. The spontaneous hydrolysis of the esters is insignificant under these conditions and can be neglected.

(Bloch and Suter, 1946). In the beginning, the reaction is a linear one; later, the curve grows more flat, yet without reaching an endpoint within twenty-four hours.

The acid quantity determined by titration is smaller than the theoretical value, owing to the fact that a part of the liberated acetic acid is oxidized by the tubercle bacilli (Cutinelli, 1940; Franke and Schillinger, 1944). As will be seen later, respiratory intensity depends on the concentration of the acetic acid present. It is obvious, therefore, that identical concentrations of the three esters are oxidized with different intensity. As shown in table 2, the bacillary enzyme liberates unequal quantities of acids within the same time unit. The optimum concentrations of mono-, di- and triacetylglycerol, thus, vary from each other.

On the other hand, conclusions as to the actual concentration of acetic acid can be drawn from the concentration of an ester at the maximum oxidation rate. These values are displayed in table 1. They correspond to 10 to 15 per cent of theoretical values and are roughly the same as the values in table 2.

(3) *Glycerol ethers:*

(a) *Glycerol-α-monoisoamylether:* When dissolved at 0.06 Mol/l. in phosphate buffer, this compound exerts a similar effect on bacillary respiration as salicylate, benzaldehyde and other substances (Bernheim, 1941; Bloch, 1944), that is, in higher concentrations the oxygen uptake is completely inhibited, but, when the concentration is reduced, it rises to a maximum. A characteristic experiment is shown in chart 2.

After having seen in the case of esters that they are split by esterases and that the promoting respiratory effect can be attributed to the liberated acid compo-

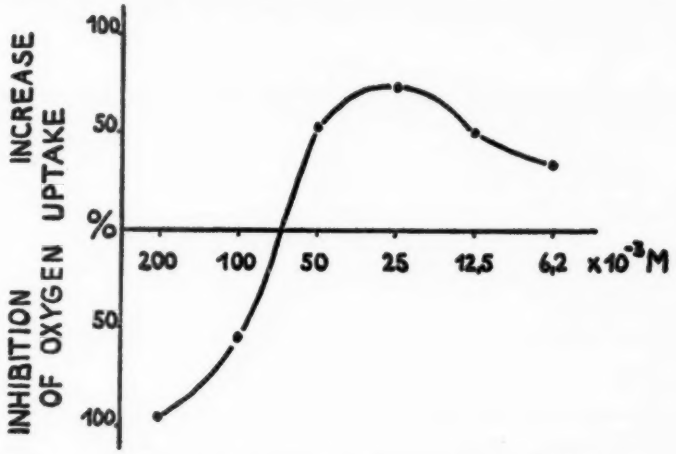

CHART 2. The effect of different amounts of isoamylic alcohol upon the oxygen uptake of tubercle bacilli.

nent, we suspected a similar behavior in the present case and tried to prove that the ether, too, can be split.

Bernheim (1941) showed that isoamylalcohol increases the oxygen consumption of tubercle bacilli. We could confirm this fact and found in addition that the respiratory rate of the ether depends on concentration just as that for the acetic acid does (see later). Identical inhibitory or promoting effects can be seen with isoamylalcohol solutions one-half to one-third as concentrated as the corresponding molar concentrations of the alcohol-glycerol-ether. This relation depends on the speed of the splitting reaction, due to the fact that only the liberated alcohol is oxidized. In one point, however, this case differs from the experiments with acetic acid or glycerol-acetic acid-esters: the oxygen uptake reached with glycerol is nowhere surpassed. According to this, the combination of glycerol with isoamylalcohol does not produce any additional effect.

(b) *Glycerol-α-monomethylether:* This compound does not exert any effect on

bacillary respiration within the limits of 0.2 to 0.001,25 Mol/l. Methanol is equally ineffective. Thus, we cannot affirm that this ether is split. We rather think it is not, otherwise the liberated glycerol should affect the oxygen consumption of the bacilli.

(*c*) *α-α-diglycerol ether:* This compound does not exert any inhibitory effect. The oxygen uptake is slightly increased to about 50 per cent of the glycerol effect with concentrations of 0.4 to 0.2 Mol/l. The increase being no greater, the ether does not seem to split and the entire compound is probably used as substrate.

(*d*) *Acetone glycerol:* This substance also increases the oxygen uptake, but less than glycerol. As in the previous case, we think that no splitting takes place, and this for two reasons: (*1*) after shaking bacillary suspensions with acetone glycerol, even for many hours, we were unable to detect any traces of acetone; (*2*) as seen in table 3, acetone when used separately exerts an inhibitory effect

TABLE 3

The effect of glycerol, acetone, and acetone glycerol upon the oxygen uptake of tubercle bacilli

SUBSTRATE	INCREASE (+) OR INHIBITION (−) OF OXYGEN UPTAKE
	per cent
—	±0
Glycerol 0.2 M	+94
Acetone glycerol 0.2 M	+96
Acetone glycerol 0.05 M	+64
Acetone glycerol 0.0125 M	±0
Acetone 0.2 M	−98
Acetone 0.0125 M	−44

on the oxidation rate. From the lack of a similar decrease, when the compound is used as a whole, we conclude that no acetone is liberated.

(*e*) *Mono- and diacetone glucose:* Unlike the corresponding glycerol compound, these substances are not utilized at all and so do not produce any effect, neither increasing nor reducing the respiration rate.

(*4*) *Other compounds:*

(*a*) *C-methylglycerol:* This substance, produced entirely synthetically, has the same effect on cell respiration as glycerol itself.

(*b*) *3-aminopropane diol:* This compound gives a strong basic reaction (pH of the 0.2 M solution in water: 10.25). Owing to this fact, respiration is inhibited. However, if neutralized, the substance exerts a slight increasing effect (25 per cent more than control with 0.2 Mol/l.).

(*c*) *Acetic acid:* This substance, too, has to be neutralized, as the increase of respiration produced by acetic acid depends on pH. An optimum appears at pH 6.1 (see chart 3). This behavior differs entirely from that of glycerol. A similar statement was made by Loebel, Shorr and Richardson (1933) when they used lactic acid and glycerol.

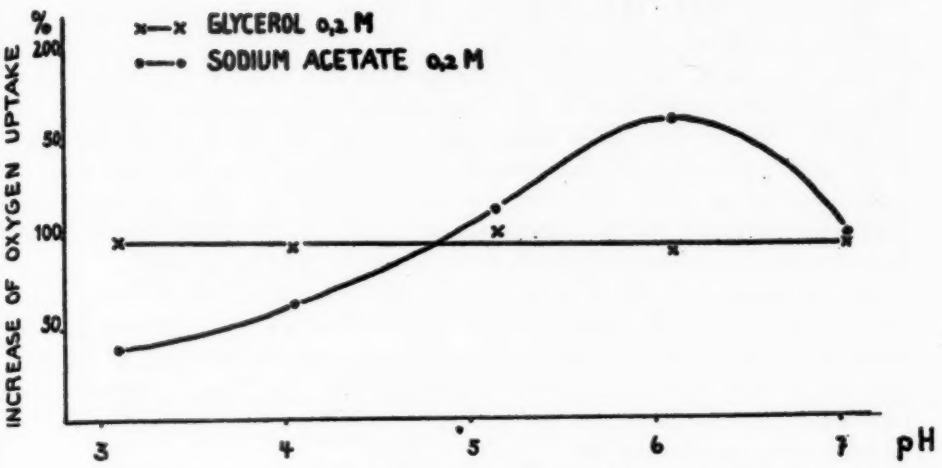

CHART 3. The oxygen uptake of tubercle bacilli with glycerol and sodium acetate at different pH values of the medium.

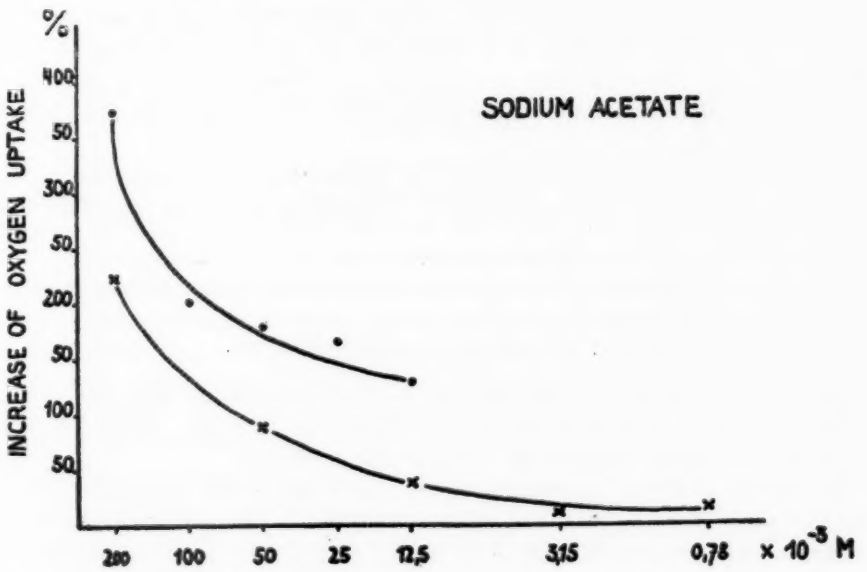

CHART 4. The effect of various concentrations of sodium acetate upon the oxygen uptake of tubercle bacilli. The two curves represent two experiments with different amounts of bacteria.

×—×: 4.7 mg. dry weight of bacteria in each Warburg-vessel.

●—●: 8.3 mg. dry weight of bacteria in each Warburg-vessel.

Moreover, the respiratory rate depends on concentration of neutralized acetic acid (or sodium acetate) and rises with the concentration of the substrate (chart 4). This behavior, too, is different from that of glycerol (Bloch, 1944).

The addition of 0.01 M KCN gives an inhibition up to 60 per cent for acetate, and less than 30 per cent for glycerol.

There are, thus, three points where glycerol and acetate respiration differ from each other: dependence on pH, dependence on concentration and inhibition by KCN. We conclude from these facts that two enzyme-systems, belonging to different types, are acting in respiration in the presence of glycerol and of acetic acid, a conclusion which is further supported by the fact that the increases in oxygen uptake due to the two substances are added one to another when optimum concentrations are combined (0.025 M for acetate; 0.2 M for glycerol).

The dependence on pH of respiration in the presence of acetate also gives an easy explanation for the concentration optima observed in the case of glycerol esters, the liberated acetic acid producing even in buffered solutions an unfavorable pH for the respiration of the microörganisms, and, thus, a concentration proves most effective that does not correspond to the real optimum concentration found in neutralized solutions.

Growth Experiments

(*1*) *Effect of substances increasing the respiration rate:* It has already been described in a previous communication (Bloch, 1946) that there is no parallelism between the promoting effect of a substance on respiration and on growth of *M. tuberculosis.* Nevertheless, in substances so closely related to glycerol, we expected to find a more corresponding behavior. As will be seen, this supposition proved wrong.

Substances to be tested were added to culture media in concentrations corresponding to glycerol, that is, 0.2 Mol/l. The media used were the following:

(*a*) Synthetic medium without glycerol.
(*b*) Synthetic medium without glycerol + 2 per cent normal human serum.
(*c*) Nutrient broth agar.
(*d*) Nutrient broth agar + 10 per cent normal horse serum.

The bacilli grown as control cultures on synthetic medium with glycerol gave in 65 experiments an average dry weight of 227.5 ± 22.3 mg. Each determination is based on the average weight of three culture flasks.

The results of these experiments show that none of the substances tested is able to replace glycerol, even to a moderate degree. The addition of substances known to promote growth, such as blood and serum, does not affect the result.

DISCUSSION

A comparison between the results of the respiration and of the growth experiments will once more confirm the fact that the action of a substance on the respiration and the action on the growth of tubercle bacilli is of a completely different order. The effects are totally dissimilar. This lack of parallelism appears to us especially impressive in the present case, because glycerol and the majority of the compounds tested are chemically so closely related. Kondo (1925) reported an experiment in which tubercle bacilli were able to grow with

acetic acid as the only source of carbon. The strain used in our experiments did not utilize acetate as nutrient, although its ability to use it for its respiratory metabolism was very marked. The lack of similarity mentioned above is even more striking in the case of methylglycerol and diglycerol ether, two compounds very similar to glycerol itself. The properties required in a substance that is to act as a growth-promoting factor seem, therefore, to be much more closely defined than those required in substances that increase respiration. A large number of different compounds are known which are able to increase the oxygen uptake of tubercle bacilli but only a few growth-promoting substances. With regard to inhibitory substances this relation is in one sense just inverted: we know a lot of compounds with inhibitory action on growth, but only a few acting as respiratory inhibitors (Bloch, 1946).

These facts confirm the finding that respiration and multiplication of the cell are two entirely different mechanisms connected only in one point: multiplication depends on an intact respiratory system, whereas respiration can function even if the multiplication apparatus is blocked. Therefore, the mechanism of multiplication seems to be more specific than the system controlling respiration: its chemical differentiating power is a better one, as demonstrated by the small number of substances acting as nutrients; its function is more sensitive and therefore easier to disturb, as shown by the comparatively important number of growth-inhibiting substances.

Apparently different experiments have led to the same conclusions concerning the character of cell growth and multiplication of *M. tuberculosis*. However, as shown by Sevag (1944), these findings may be essentially the same when we come to microörganisms other than tubercle bacilli. Yet there is one difference: accessory growth factors which play an important part in growth experiments with other microörganisms are not known to affect *M. tuberculosis*. The experiments with synthetic glycerol have not suggested an eventual importance of similar still unknown substances. Nevertheless the findings of Drea (1942, 1944) must be taken into account; even with all possible precautions the necessary quantity of the inoculum is still considerable as compared with that of other microörganisms. We cannot, in any event, exclude the action of accessory growth factors that are, so far, unknown.

Our experiments do not explain the nature of the extraordinary part played by glycerol as nutrient in the metabolism of *M. tuberculosis*, but they rather confirm it, showing the specificity of this compound when compared with the action of chemically closely related substances.

SUMMARY

1. The influence of 12 different compounds, chemically related to glycerol, upon the respiratory metabolism and the growth of tubercle bacilli was investigated. The majority of the substances increased the oxygen uptake of the bacilli, but none was able to replace glycerol as nutrient in a synthetic medium.

2. Several esters and ethers can be split by an enzymatic action of the bacilli and their liberated constituents further utilized in the bacterial metabolism.

3. Many substances of different chemical nature are able to increase the oxygen uptake of tubercle bacilli, but this action often depends on the concentration of the substances and the pH of the medium, whereas glycerol was found to be much less affected by these factors.

4. Additional effects on the bacterial respiration can be seen if glycerol is combined with acetic acid, but not with isoamylic alcohol, although both acetic acid and isoamylic alcohol increase the oxygen consumption of the bacilli. From this fact it can be concluded that the oxygen consumption of tubercle bacilli may be based on different respiratory mechanisms.

5. The results of the experiments confirm that respiration and growth depend on two different metabolic systems. The latter seems to be more specific as to the metabolites which can be utilized.

SUMARIO

1. Investigóse el influjo de 12 distintos compuestos, químicamente enlazados con el glicerol, sobre el metabolismo respiratorio y la proliferación de los bacilos tuberculosos. La mayoría de las sustancias acrecentaron la absorción de oxígeno por los bacilos, pero ninguna pudo suplantar al glicerol como nutriente en un medio sintético.

2. Mediante una acción enzimática de los bacilos, pueden disolverse varios ésteres y éteres, y utilizarse ulteriormente sus componentes liberados en el metabolismo bacteriano.

3. Muchas sustancias de diversa naturaleza química pueden reforzar la absorción de oxígeno por los bacilos tuberculosos, pero esa acción depende a menudo de la concentración de las sustancias y del pH del medio, en tanto que el glicerol se vió mucho menos afectado por dichos factores.

4. Pueden observarse nuevos efectos sobre la respiración bacteriana si se combina el glicerol con ácido acético, pero no con alcohol isoamílico, aunque tanto el ácido como el alcohol acrecientan el consumo de oxígeno de los bacilos, de lo cual cabe deducir que el consumo de oxígeno por los bacilos tuberculosos puede basarse en distintos mecanismos respiratorios.

5. El resultado de los experimentos confirma que la respiración y el crecimiento dependen de dos distintos sistemas metabólicos, pareciendo el último más específico en cuanto a los metabolitos utilizables.

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INFLUENCE OF SULFASUXIDINE AND SUCCINIC ACID UPON THE TUBERCLE BACILLUS[1]

MICHELE GERUNDO[2]

The observations described in this paper were made in the course of some experimental work which was carried out in an attempt to ascertain whether sulfasuxidine had any bacteriostatic action upon *Mycobacterium tuberculosis*. It was assumed that slow growing bacteria would be more easily influenced by sulfonamides inasmuch as the drug would inhibit growth or division of cells before it begins. Previous experiments had shown that sulfathiazole inhibits the growth of the bacilli *in vitro*. Six different strains of *M. tuberculosis* were used in the experiments, 3 of them being chromogenic varieties.

Incidentally, when culture was carried on bouillon-glycerol, in presence of sulfasuxidine, the pellicle fell rapidly to the bottom and grew alongside the walls of the tube. Microscopic examination revealed long granular rods and beaded forms in the culture tubes containing sulfasuxidine, whereas it showed only short plump rods in the controls.

The addition of para-aminobenzoic acid stimulated growth and pigment production in all the strains with the exception of one which showed growth in the tube containing sulfasuxidine but no growth in the presence of para-aminobenzoic acid alone.

In order to avoid the influence of any substance which could be considered antagonistic to sulfonamides, Long's synthetic medium was chosen. The bacillus grows very slowly in this medium and usually only when heavy inoculum is used. Six tubes were inoculated for each strain used.

Much to our surprise the growth was abundant in tubes containing sulfasuxidine and still better when sulfasuxidine and para-aminobenzoic acids were present in the same tubes. Para-aminobenzoic acid alone did not stimulate such abundant growth as when it was combined with sulfasuxidine, but production of pigment was definitely more abundant in its presence. Whether it played a rôle in the formation of pigment is not clear, as even strains which did not form pigment on ordinary media formed pigment in its presence.

It was assumed that probably growth in the presence of sulfasuxidine was due to the succinic acid radical present in the drug. Such hypothesis was based on the knowledge that asparagine, which is necessary in the synthetic medium to support growth, is metabolized by the bacteria to succinic acid, and utilized as such as a source of energy for growth.

Long (6) in his work on the metabolism of the tubercle bacillus had already found that ammonium salts of dibasic acids supported good growth. Ammonium succinate and the ammonium salts of malic and tartaric acids, which are hydroxy acids from succinic acid, were found to be good substrates for the growth of the bacillus. By clever intuition he anticipated that the metabolism of the

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tubercle bacillus may follow a path—perhaps identical with what is now known as the Szent-György or Krebs cycle—in which succinic acid is an important link in the chain.

In consequence, sodium succinate and para-aminobenzoic acid were added to the medium containing asparagine. The growth was more abundant than in tubes without succinate, but the rôle of para-aminobenzoic acid was not clearly established, as its addition did not appear to be essential for the development of the bacteria.

Finally, asparagine was excluded entirely and Long's medium was modified as follows:

Ammonium citrate	10 g.
Potassium acid phosphate	3 g.
Sodium carbonate, anhydrous	3 g.
Sodium chloride	2 g.
Magnesium sulphate	1 g.
Ferric ammonium citrate	0.05 g.
Sodium succinate	10 g.
Glycerol	50 g.
Water to 1000 cc.	

5 cc. of a 1:1000 solution of para-aminobenzoic acid was added for every 100 cc. of medium.

In this medium the growth of mycobacteria was more abundant than in ordinary Long's medium and to a certain extent more rapid. There was no difficulty for successive transplants in this medium. Para-aminobenzoic acid was not essential to growth, as its rôle was apparently concerned only with the production of pigment.

Table 1 summarizes the results of the various cultures carried out on the original Long's medium and on its modified form. It is seen from it that Long's medium without asparagine is unable to support growth, but its modified form with sodium succinate gave more abundant growth than the original medium.

It is rather difficult to formulate a clear idea of the action of sulfonamides upon tubercle bacilli. *A priori*, given the nonspecific action of sulfonamides upon bacteria, it should not be surprising that they do exert a bacteriostatic influence upon the bacterium. Assuming that sulfonamides inhibit growth and division (and there is an extensive literature to prove it) the tubercle bacillus should be suitable for experimentation, because of its very slow growth. Fitzgerald and Feinstone (1), in correlating the antibacterial activity of sulfonamides with their acid dissociation constants and their ability to withstand the inhibitory action of para-aminobenzoic acid, extended the theory of nonspecificity of sulfonamides to include their effect on the tubercle bacillus.

Bazzicalupo (2) noted that sulfonamide at a concentration of 8 mg. per cent had bacteriostatic effect upon the tubercle bacillus.

Even in the experimental therapeutic field Greey, Campbell and Culley (3) obtained good results with sulfanilamide in experimental tuberculosis of the guinea pig, if given early before spreading began. Other authors have obtained similar results with various compounds.

Mayer (4) has described a yellow pigment formed by a special strain of *Mycobacterium tuberculosis, var. hom.*, in the presence of para-aminobenzoic acid or procaine. The formation of this pigment involves a specific oxidase; the pigment is an unstable product of para-aminobenzoic acid and contains oxidized NH^2 groups. He found that 1:1000 sulfanilamide completely inhibited growth of the bacilli. When para-aminobenzoic acid was added, then sulfanilamide in various concentrations either inhibited completely or decreased the formation of the yellow pigment. The inhibition may be due to inactivation of an essential metabolite as the result of reaction between sulfonamide and para-aminobenzoic acid, but it seems more likely that it is of enzymatic nature, the sulfonamide directly poisoning the enzyme.

TABLE 1

Growth of tubercle bacilli on modified Long's media

*STRAINS OF TUBERCLE BACILLI:	A	B	C	D	E	F
Long's medium	+	+	+	+	+	+
Long's medium without asparagine	?	−	−	−	−	−
Long's medium with sulfasuxidine	+±	+±	+	+	+	+±
Long's medium with sulfasuxidine and para-aminobenzoic acid	+⊦	++	+	+	+	++
Long's medium with para-aminobenzoic acid	+±	+±	+	+	+	+
Long's medium with sodium succinate	++	⊦+	+±	⊦±	+±	++
Long's medium with sodium succinate and para-aminobenzoic acid	++	++	+±	+±	+±	++
Modified Long's medium with sodium succinate	++	++	+±	+±	+±	++
Modified Long's medium with sodium succinate and para-aminobenzoic acid	⊦+	++	+±	+±	+±	++

* All the strains were isolated from human cases except F which was furnished by Ely Lilly and Company.

Our results with sulfasuxidine are at variance with those of the authors already mentioned and with our previous tests with sulfathiazole. It is true that an action exercised by one sulfonamide must not be entirely similar to that of any other sulfonamide; in this respect, results are not strictly comparable. In using a conjugated sulfonamide, succinyl-sulfathiazole, growth was definitely more luxuriant in presence of the drug than on ordinary Long's medium. That the tubercle bacillus is capable of utilizing succinic acid as a substrate is already well known; its ability to grow on Long's medium very likely is due to the fact that the medium contains asparagine, which is broken down to succinic acid, and glycerol, which may also form succinic acid under certain conditions (5). The chromogenic strains used in our experiments, produced pigment in presence of para-aminobenzoic acid alone or combined with sulfasuxidine; there was actually no interference or antagonism.

The substitution of asparagine with succinic acid alone or combined with para-aminobenzoic acid proves in our experiments definitely that the tubercle bacillus is capable of utilizing this acid as a substrate. The rôle of asparagine may be explained by the fact that succinic acid which is a structural part of

both amide-N and amino-N is the real factor in the acceleration of bacterial growth.

SUMMARY

The addition of sulfasuxidine to bouillon-glycerol did not inhibit the growth of the tubercle bacillus, but induced development of long granular rods and beaded forms.

When Long's synthetic medium was used, the bacteria grew more abundantly in the tubes containing sulfasuxidine, either alone or with para-aminobenzoic acid.

On the assumption that the succinic acid radical present in sulfasuxidine was the factor stimulating growth, the bacteria were cultured in a modified synthetic medium, in which sodium succinate was substituted for asparagine; this modified form supported better growth than the original medium.

It seems reasonable to conclude that asparagine is not necessary for growth as a source of amide-nitrogen and amino-nitrogen and that succinic acid, which is the structural element of both forms of nitrogen, is the factor involved in the development of the bacterium. Para-aminobenzoic acid was not essential for growth, but its rôle was concerned with the formation of pigment.

SUMARIO

Cultivo del Bacilo Tuberculoso

La adición de sulfasuccidina al caldo-glicerina no inhibió el crecimiento del bacilo tuberculoso, pero sí hizo proliferar bastoncillos granulares largos y cuerpecillos moniliformes.

Al emplear el medio sintético de Long, las bacterias se desarrollaron con mayor abundancia en los tubos que contenían sulfasuccidina, ya sola o combinada con ácido para-aminobenzoico.

Partiendo de la suposición de que el radical de ácido succínico presente en la sulfasuccidina era factor estimulador del desarrollo, las bacterias fueron cultivadas en un medio sintético modificado, en el cual se empleó succinato de sodio en vez de asparagina; esta fórmula modificada mostró un desarrollo mejor que el medio primitivo.

Parece lógico deducir que la asparagina no es necesaria para el desarrollo como fuente de amido-nitrógeno y amino-nitrógeno, y que el ácido succínico, que es el elemento estructural de ambas formas de nitrógeno, es el factor que interviene en el desarrollo de la bacteria. El ácido para-aminobenzoico no fué esencial para el desarrollo, pero sí intervino en la pigmentogenia.

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CULTIVATION OF TUBERCLE BACILLI FROM GASTRIC JUICE[1]

A Study of the Factors Affecting the Cultivation of *Mycobacterium tuberculosis* from Gastric Juice

VERA VINCENT AND EDWARD A. BIRGE

During the past fifteen years many authors have shown that aspiration of the contents of the fasting stomach is a practical method for the diagnosis of tuberculosis in children and in patients producing scanty amounts of sputum. Recently, however, several papers have appeared which cast serious doubt upon the value of this diagnostic procedure when cultures are not made immediately after the specimen is collected.

Originally described by Meunier in 1898 (1), diagnostic gastric lavage was reintroduced by Armand-Delille (1a) in 1927. At first only smears, made after digestion and concentration of the stomach contents, were employed. Later, Poulsen *et al.* (6) used guinea pig inoculations and cultures to make the method more sensitive. Examination of the early literature fails to show that anyone carried out experiments to determine the possible effect of gastric juice on the tubercle bacillus. It was generally believed that acid had little effect on the viability of the bacillus although the literature did not justify this assumption. In 1889 Straus and Wurtz (10) reported that, although the gastric juice of dogs would not destroy tubercle bacilli after contact for one to six hours, contact for eight to twelve hours would produce some attenuation of the organisms' virulence for guinea pigs, while an exposure of eighteen to thirty-six hours killed the organisms. Inkster and Gloyne (3) showed that tubercle bacilli would retain their virulence for guinea pigs after exposure to normal gastric juice for two hours, but they did not study the effect of a longer period of time. Roper and Ordway (7), in contrast to most of the workers, stated that tubercle bacilli were only slightly inhibited by contact with one-tenth normal hydrochloric acid for four days. Details of the experiment are not given. Floyd and Page (2) suspended tubercle bacilli in an artificial gastric juice for periods varying from three to twelve hours. The suspensions were kept at incubator temperature and subsequently guinea pigs were inoculated. A three-hour exposure had no effect on the bacilli, but exposure to the gastric juice for six and twelve hours produced a marked lessening of the number of lesions found in the animals. Exposure to filtered duodenal contents had no effect on the virulence of the organisms.

Recently, Schwarting (8) has reported that placing gastric aspirations in the ice box or allowing them to stand at room temperature for one to two days produces a considerable number of false negative reports. She is inclined to attribute this result to the presence of an inhibitory substance, described by Piasecka-Zeyland (5), in the saliva swallowed during the passage of the stomach tube. Kramer (4) mixed heavily positive sputa with normal gastric juice and incubated the mixture at 37°C. for varying periods of time. The tubercle

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bacilli were able to withstand this treatment for ten hours, but after twenty-one hours the mixture was no longer pathogenic for guinea pigs. He assumed that gastric lipase or pepsin was responsible for killing the organisms. Sprick and Towey (9) divided 33 gastric aspirations into three equal parts. One portion was cultured and inoculated into a guinea pig at once, the second and third portions were allowed to stand at room temperature for twenty-four and forty-eight hours, respectively, and then treated in the same manner as the first portion. Seventy-three per cent of the specimens examined immediately were positive by one or the other method, 45 per cent were positive after standing for twenty-four hours, while only 21 per cent were positive after standing for forty-eight hours.

For many years this laboratory has been receiving gastric aspirations for the diagnosis of tuberculosis from most of the sanatoria in Wisconsin as well as from many general hospitals and private doctors. These specimens represent both single aspirations and three-day poolings. Allowing for twenty-four to forty-eight hours in transit, our specimens are two to five days old by the time they arrive at the laboratory. The appearance of these recent papers demonstrating the fact that a high percentage of false negatives may occur when gastric aspirations are allowed to stand was disturbing. Accordingly, we have undertaken a study to determine the nature of this inhibitory substance and to determine what corrective measures could be applied to counteract it.

MATERIALS AND METHODS

Two types of specimens were employed—gastric aspirations from known tuberculous patients and normal gastric juice seeded with cultures of tubercle bacilli freshly isolated from sputa or spinal fluids. No organisms obtained by culture of gastric contents were used for seeding in order to eliminate any possibility of strain adaptation to gastric juice. These experimental specimens were handled in the same way as our routine specimens. They were concentrated by sodium hydroxide digestion with subsequent centrifugation and neutralization. The entire sediment was distributed over the surface of one tube of Hohn's and one of Petragnani's medium. No guinea pigs were inoculated, since unpublished data in our laboratory as well as many papers in the literature show that approximately the same number of positives are obtained by each method. The cultures reported as positive all had the colony appearance typical of *M. tuberculosis*.

EXPERIMENTAL

The pH of 799 routine gastric aspirations received from all over the state was determined by means of thymol blue and methyl orange indicators supplemented by nitrazine paper. The range of pH values was found to vary from 2 to 8. No specimen had a pH value above 8.5. A small number of specimens were more acid than pH 2, but we had no practical method of determining pH values in this range. Pepsin was determined on many of these specimens by Nirenstein and Schiff's modification of Mett's method (11). We found that a low pH was invariably associated with large amounts of pepsin while specimens which were neutral either had no pepsin or a very negligible amount. There was no correla-

TABLE 1

Percentage of positive cultures obtained from routine gastric aspirations

pH OF SPECIMEN	NUMBER OF SPECIMENS	PER CENT POSITIVE CULTURES	PER CENT CONTAMINATED CULTURES
2	90	1.1	6.7
2.5	61	1.6	0
3	100	4	2
4	78	7.8	1.3
4.5	45	6.6	2.2
5	103	3.9	4.9
6	57	12.3	8.8
7	126	16.7	13.5
7.5	74	14.9	19.0
8	65	9.2	21.5

TABLE 2

Effect of pH on the survival of tubercle bacilli in vitro

NUMBER	BACILLI SUSPENDED IN	SUSPENSION KEPT AT	IMMEDIATE CULTURE	SUBSEQUENT CULTURES IN DAYS						
				1	2	3	4	5	6	7
71621	Broth, pH 2.5	Room temperature	+++* 33	+ 32	—	—	—			
73089			++++ 29	+++ 29	+++ 29	++ 29	+ 35			
67607	Buffer, pH 2.5	Ice box	++++ 18		+ 39		—			
65212			++++ 28		++++ 26		—			
67644			++++ 18		++ 33		—			
73088	Broth, pH 6.2	Room temperature	+++ 29	+++ 28	+++ 27	+++ 26	+++ 25			
71620			++++ 24	++++ 23	++++ 22	++ 32	+ 31			
67607	Buffer, pH 6.2	Ice box	++++ 18		++++ 25		++++ 23			++ 20
65212			++++ 18		++++ 26		++++ 37			++++ 35
67644			++++ 25		++++ 23			++++ 20		

* Arabic numerals designate day growth was first observed.

Plus signs indicate average amount of growth on 2 tubes of media:

\+ 1 to 15 colonies
++ 15 to 30 colonies
+++ 30 to 50 colonies
++++ over 50 colonies

tion between the amount of mucus in the specimen and the results of the culture. Reference to table 1 will illustrate the relation between the acidity of the specimen and the number of positive cultures obtained. The presence of a pH lower than 6 apparently renders the specimen useless if it has stood for any length of time. These routine gastric aspirations represent specimens obtained from persons with incipient tuberculosis or from patients convalescent at the various sanatoria or rest camps, so that a high percentage of positive cultures is not to be expected. One complication found in this study is the increased percentage of contaminations which occur as the pH of the specimen increases.

Suspensions of tubercle bacilli were made in a phthalate-HCl buffer rendered isotonic with 0.5 per cent saline and in tryptone broth. The acidity of both

TABLE 3

Influence of pH and environment on cultures made from gastric aspirations

pH OF SPECIMEN	NUMBER OF SPECIMENS	SECOND PORTION HELD	GROWTH OF SECOND CULTURE		
			Same amount as original culture	Diminished	None
6 or above	5	Ice box	4	0	1
4–6	9	3–4 days	7	2	0
below 4	8		2	3	3
6 or above	3	Room temperature	1	0	2
4–6	1	3 days	0	0	1
below 4	9		0	1	8
6 or above	5	Ice box 3 days	3	2	0
4–6	8	then	0	0	8
below 4	8	Room temperature 2 days	0	1	7

suspending media was adjusted to pH values of 2.5 or 6.2. These suspensions were heavy enough so that a loopful of the mixture gave an abundant growth on the culture media used. Table 2 illustrates the results which were obtained. Fairly rapid killing of the organisms, as measured by the amount of growth on cultures, occurred in the acid specimens, but the number of bacilli failed to decrease greatly when a neutral suspending fluid was used. The temperature at which the suspensions were kept played little part in determining the length of survival.

A series of artificially inoculated, normal gastric aspirations and gastric aspirations from tuberculous patients were also examined. These specimens, regardless of origin, were thoroughly mixed by shaking by hand and then divided into two parts. The first portion was cultured at once. The second portions were cultured either after standing at room temperature for three days, after being in the ice box for three days or after being placed in the ice box for three days plus two days at room temperature for a total of five days. In addition, 3 specimens

TABLE 4

Effect of preliminary neutralization on cultures

SPECIMEN	PEPSIN VALUES	IMMEDIATE CULTURE	SECONDARY CULTURES†	
			pH 6.5–7.0	pH 2.0–3.0
66735	1064	++++* 27	++++ 31	+ 42
82185	400	++++ 36	+ 56	—
87204	0	+ 48	—	—
87701	256	++++ 23	+ 23	—
88559	324	++++ 21	+ 30	—
89186	324	+ 44	+ 44	—
91186	256	++ 47	++ 35	—
91187	256	++++ 29	++++ 35	1 col.* 49
91188	144	+++ 29	++++ 24	1 col.* 42
91890	450	+++ 38	—	—
91891	635	++++ 27	+++ 34	—
94352	1124	1 col.‡ 40	—	—
94896	0	—	+ 33	—
94897	400	++ 46	+ 48	—

* See table 2.

† Secondary cultures made after standing in ice box for two days, then in room temperature for three days.

‡ One tube only showed a single tuberculosis colony.

were divided into two parts and both cultured at once; these specimens gave identical results with both cultures. Table 3 shows the results of this experiment. The detrimental effect of high acidity is clearly evident. Storage at ice box temperatures apparently slows the process somewhat. With a few neutralized specimens we found that there was no difference between the first and second cultures, even when the second portion was allowed to stand in the ice box for five days before cultures were made.

Finally, 14 gastric aspirations were divided into three equal parts. One portion was cultured at once. The second portion was brought to a pH of 2 to 3, by means of hydrochloric acid if necessary, while the third portion was brought

TABLE 5

Effect of pepsin on vivability of tubercle bacilli

CULTURE	AMOUNT PEPSIN	SUSPENSION KEPT IN	IMMEDIATE CULTURE	SECOND CULTURE-DAYS	
				2	5
64018	256	Ice box	++++* 42	++++ 40	++ 40
85451	538		++++ 30	++++ 36	++ 37
67068	1024		++++ 25		+ 37
64018	256	Room temperature	++++ 42	++++ 40	+ 36
85451	538		++++ 30	+ 40	—
67068	1024		++++ 25		+ 37

* See table 2.

to a pH of 6.5 to 7.0 by the use of sterile one-tenth normal sodium hydroxide, if necessary. The second and third portions were then placed in the ice box for two days plus three days at room temperature for a total of five days after which they were concentrated and cultured as usual. This time interval was chosen in order to simulate the conditions under which we receive the majority of our specimens. Table 4 gives the experimental details. The neutral portion of the gastric specimen clearly gives better results than the acid portion.

This last experiment indicates that the pepsin content of the specimen plays only a secondary rôle in determining the survival of tubercle bacilli. This was confirmed by suspending tubercle bacilli in saline to which varying amounts of dried pepsin were added. The pepsin activity was determined by the egg-white digestion technique mentioned previously. Table 5 indicates that the survival

of the organisms over a five-day interval of time was fairly satisfactory. The pH of these suspensions varied between 5 and 6.

DISCUSSION

The experimental work reported in this paper points to only one conclusion. The tubercle bacillus, although it is amazingly resistant to high degrees of acidity, is not able to withstand contact with hydrochloric acid indefinitely. Survival of the bacilli in the stomach contents depends on the amount of free acid present in the specimen. The length of survival in an acid medium, however, can be modified by the temperature at which the specimen is kept. Since the destructive process is slowed in the cold, we believe that pepsin digestion in an acid medium hastens the killing of the bacilli when the specimen is allowed to stand at room temperature. Strain variation in respect to acid resistance has not been studied.

The experimental evidence also shows that in neutral gastric juice the tubercle bacillus will usually survive for at least five days. Here again survival is best at refrigerator temperatures although the difference is less marked. The occasional poor results are probably due to the killing of the tubercle bacillus by other bacteria or by the process of concentration. The latter supposition is the most likely.

It is obvious that the techniques now in general use must be modified if we are not to obtain a large number of false negative reports. Prompt culturing of the specimen after it is collected would be ideal. Local laboratory conditions, however, will modify this ideal arrangement because of shortages of personnel and money. Few laboratories are able to double or triple their work in order to make separate daily cultures in place of a single culture of a two- or three-day gastric pooling. The necessity of multiple cultures or pooling is illustrated by the fact that in the course of this study 21 patients on the tuberculosis service had gastric lavages on two or three successive days. Each aspiration was cultured separately as soon as it reached the laboratory. Ten patients were consistently negative, 8 were consistently positive, while in 3 cases both positive and negative cultures were obtained.

It is our belief that for practical purposes gastric aspirations may still be collected and pooled over a period of two or three days if the specimen is kept in the ice box continuously and if the pH of the specimen is brought to approximate neutrality. Reference to table 1 shows that preliminary neutralization is not without its drawbacks. As the pH of the specimen increases, the number of positive cultures also increases, but the incidence of contaminated cultures increases at the same time. These contaminations are due to the rapid growth of bacteria, especially spore forming bacilli and fungi, during the period that the specimen stands. These bacteria cannot be entirely eliminated by the sodium hydroxide digestion because the prolonged contact with strong alkali necessary for their destruction will also kill the tubercle bacillus. Ordinarily, most of this contaminating growth is held in check by the acidity of the specimen. Where the specimen can be continuously refrigerated, preliminary neutralization to a pH

value of 6.5 to 7.0 is the best procedure. However, where specimens are sent to a central laboratory or must stand at room temperature for several hours, we feel that the pH should only be brought to about 6.0. The difference in the number of positive cultures obtained at this pH as compared with the number obtained with specimens at a pH of 7 is small, but the percentage of contaminated cultures is definitely less at the lower pH. When specimens are sent to a central laboratory, it will probably be impossible to avoid false negative cultures, but preliminary neutralization of the specimen prior to mailing should improve the results obtained.

SUMMARY

1. A study has been made to ascertain the factors which influence the survival of tubercle bacilli in gastric juice.

2. Survival of the tubercle bacillus depends on the acidity of the gastric juice. The more acid the specimen, the shorter is the survival time.

3. To eliminate false negative reports, gastric specimens should be examined immediately either by cultures or by guinea pig inoculation.

4. Neutralization of gastric specimens will allow the tubercle bacillus to live several days if the specimens cannot be examined at once.

SUMARIO

1. En este estudio tratóse de averiguar qué factores afectan la sobrevivencia de los bacilos tuberculosos en el jugo gástrico.

2. La sobrevivencia del bacilo tuberculoso depende de la acidez del jugo gástrico: mientras más ácido el ejemplar, menor la duración de la sobrevivencia.

3. A fin de eliminar enfermos seudonegativos, hay que examinar los ejemplares gástricos inmediatamente, bien por medio de cultivos o de inoculaciones en el cobayo.

4. La neutralización de los ejemplares gástricos permitirá que el bacilo tuberculoso viva varios días si no pueden examinarse los ejemplares en el acto.

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